Palladium-Catalysed Migratory Suzuki-Miyaura Cross-Coupling

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“Chemistry is necessarily an experimental science: its conclusions are drawn from data, and its principles supported by evidence from facts.”

Michael Faraday

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Abstract

The installation of a functional group at a specific site through transition-metal catalysed C-H functionalisation has emerged as a powerful tool for the synthesis of complex structures in a step-economical manner. In this context, the remote functionalisation through migration of a transition-metal catalyst along an alkyl-chain, termed chain-walking, has gained significant momentum during the last decade.

The strategy developed by the group of Baudoin relies on palladium-catalysed ligand-controlled chain-walk with enolates or organozinc compounds as nucleophiles, where a site-selective reductive elimination is the terminating step. More recently, the group reported the development of a regioconvergent functionalisation of a regioisomeric mixture of bromoalkanes through a migratory Barbier-Negishi cross-coupling. However, the design of a migratory version of the ubiquitous Suzuki-Miyaura cross-coupling has remained elusive, although various palladium-catalysed migratory cross-coupling reactions were reported.

In this optic, we first investigated a one-pot approach for the hydroboration of a regioisomeric mixture of linear alkenes and subsequent terminal-selective palladium-catalysed Suzuki-Miyaura cross-coupling. The developed reaction conditions furnished excellent regioselectivity, but the yields were not satisfactory.

We then developed a benzylic-selective palladium-catalysed Suzuki-Miyaura cross-coupling based on the previous observations made. Excellent regioselectivity for the benzylic position of the initial alkene was achieved by the combination of ligand and electrophile. We also demonstrated the regioconvergence from regio- and geometrical isomeric mixture of alkenes, and long-range migration. Additionally, a mechanistic study was also performed.

Finally, we also explored the feasibility of combining the previous benzylic-selective migratory cross-coupling with a subsequent C(sp^2)-H activation in a cascade process. However, our findings led to the conclusion that the necessary presence of water for the first step is detrimental for the second.

Keywords: C-C coupling, C-H functionalisation, chain-walking, palladium, regioconvergence, remote functionalisation

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Abbreviations

Ac	Acetyl
Ad	Adamantyl
Alk	Alkyl
Ar	Aryl
BAR_F	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
b/l	branched/linear
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Cat.	Catalytic
CMD	Concerted Metalation-Deprotonation
CN	Nitrile
CO	Carbon monoxide
cod	1,5-Cyclooctadiene
COgen	9-Methylfluorene-9-carbonyl chloride
Cy	Cyclohexyl
Cyp	Cyclopentyl
DABCO	1,4-Diazobicyclo[2.2.2]octan
Dba	Dibenzylideneacetone
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DCPE	Bis(dicyclohexylphosphinoethane)
DFT	Density functional theory
DG	Directing group
DIAD	Di*iso*propyl azodicarboxylate
DMAC	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin-Periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
ee	Enantiomeric excess
equiv	Equivalent
er	Enantiomeric ratio
es	Enantiospecificity
ESI-MS	Electrospray ionisation coupled with mass spectrometry
Et	Ethyl
FCC	Flash column chromatography

FG	Functional group
FID	Flame ionisation detector
GC	Gas chromatography
GC-FID	Gas chromatography coupled with flame ionization detector
GCMS	Gas chromatography coupled with mass spectrometry
Hex	*n*-Hexyl
HPLC	High-performance liquid chromatography
*i*Pr	*iso*-Propyl
iso	isomer
L	Ligand
L_n	Unspecified amount of ligand(s)
Me	Methyl
MIDA	*N*-methyliminodiacetic acid
MM	Molecular mechanics
Ms	Mesylate
*n*Bu	1-Butyl
n.d.	not determined
Nf	Nonaflate
NHC	*N*-heterocyclic carbenes
NMO	*N*-methyl-morpholine
NMP	*N*-methyl-pyrrolidine
NMR	Nuclear magnetic resonance
n.o.	not observed
nP	Neopentyl
OA	Oxidative addition
OAc	Acetate
OBBD	9-oxa-10-borabicyclo[3.3.2]-decane
OPiv	Pivalate
OTf	Triflate
PET	Petroleum ether
PG	Protecting group
Ph	Phenyl
Phen	Phenyl
Pin	Pinacol
Piv	Pivaloyl
PMP	para-Methoxyphenyl
Quant	Quantitative
RI-NMR	Rapid injection nuclear magnetic resonance
sec	Secondary
*s*Bu	*sec*-Butyl
S_E	Electrophilic substitution
SM	Starting material

SMC	Suzuki-Miyaura cross-coupling
Sp	Sparteine
TBA	Tetra-butyl-ammonium
TBACl	Tetra-butyl-ammonium chloride
TBAF	Tetra-butyl-amminium fluoride
$TBABr_3$	Tetra-butyl-ammonium tribromide
*t*Bu	*tert*-Butyl
TBS	*tert*-Butyldimethylsilyl
tert	Tertiary
TES	Tri-ethyl-silyl
THF	Tetrahydrofuran
THP	Tetryhydropyran
TIPS	Tri-*iso*propyl-silyl
TMEDA	Tetramethylethylenediamine
Ts	Tosyl
UV	Ultra violet
9-BBN	9-Borabicyclo[3.3.1]nonan
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane

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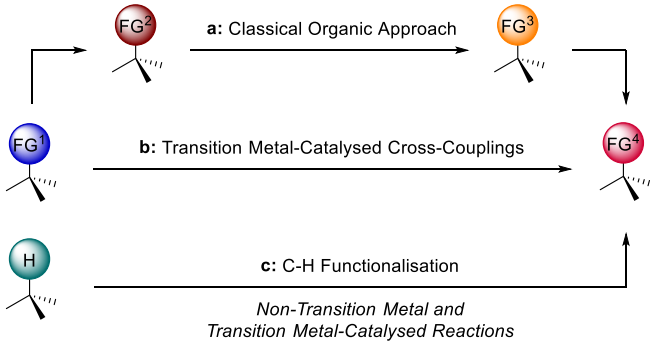
1. General Introduction

1.1. From Vitalism to C-H Functionalisation

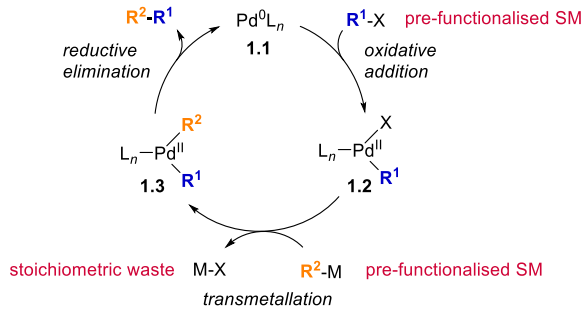
The birth of organic chemistry can be traced back to the nineteenth century with the unanticipated preparation of urea from inorganic materials by Friedrich Wöhler in 1828,[1] challenging the then generally accepted vitalism doctrine that all organic materials are endowed with vital force. In retrospect, the *coup de grace* of vitalism was arguably the synthesis of acetic acid starting from carbon disulphide by Hermann Kolbe in 1845.[2] Since then chemists have developed an impressive catalogue of reactions for the synthesis and derivatisation of organic compounds, relying on the transformation of functional groups or structural features with high chemical reactivity (Scheme **1.1a**). The developed methods can solve many chemo-, regio-, diastereo- and enantioselectivity issues but generally need pre-functionalised starting materials, obtained after several iterative steps which often require the use of a stoichiometric amount of reagents, in other words with a poor overall synthetic efficiency.[3–5] Growing concerns of limited availability of raw materials as well as climate change issues incited chemists to develop more efficient and environmental benign alternatives.



Scheme 1.1: Different strategies for the functionalisation of organic compounds.

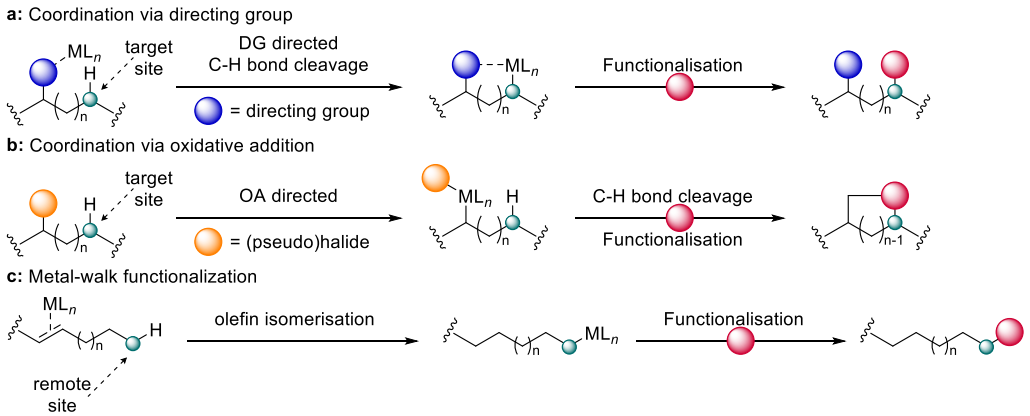
The development of transition metal-catalysed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged since the early 80s as an essential synthetic tool, allowing for the efficient combination of a wide range of coupling partners (Scheme **1.1b**). This approach enhanced considerably the ability of synthetic chemists to assemble complex frameworks between functionalised and sensitive substrates, thus providing new opportunities in total synthesis, medicinal and process chemistry as well as in biology and nanotechnology.[6–8] Prominent among these, palladium-catalysed cross-couplings witnessed an incredible growth of interest in academia and industry as emphasized by the continuously rapidly growing literature and industrial applications in this field. This was also proved by the fact that Richard Heck, Ei-ichi Negishi and Akira Suzuki were attributed the Nobel Prize in Chemistry 2010 for their roles in the discovery and development of these strategies.[9–11]

Generally, these type of reactions are initiated by the oxidative addition of a Pd^0 complex **1.1** into a carbon-(pseudo)halide bond generating an electrophilic Pd^{II} organometallic species **1.2**, which then undergoes transmetalation with a nucleophilic organometallic compound resulting in the Pd^{II} complex **1.3**. Reductive elimination of this palladium intermediate furnishes the cross-coupled product while regenerating the Pd^0L_n catalyst (Scheme **1.2**). Despite the aforementioned advantages, some limitations such as the pre-functionalisation of the starting materials and the generation of stoichiometric, often toxic, metal waste remained. Thus, further stimulating chemists to explore the direct functionalisation of C-H bonds.



Scheme 1.2: Simplified general catalytic cycle for palladium catalysed cross-coupling reactions.

The replacement of an unactivated C-H bond with a functional group, termed C-H functionalisation, is a highly desirable yet difficult step- and atom-economical synthetic approach (Scheme **1.1c**), and thus has been under intense investigations in the last two decades.[12,13] While C(sp^2)-H functionalisation has grown into a mature tool, the extension to alkyl C-H bonds has proven to be more challenging due to the ubiquity, which prevents the regioselectivity, and lower reactivity of these C-H bonds towards organometallic bond cleavage.[14–19] Nevertheless, selective alkyl C-H functionalisation can be facilitated by pre-complexation strategies where the substrate coordinates to the metal complex prior to the selective C-H bond cleavage, resulting in a lower activation barrier. Therefore, the substrate becomes ligand, which brings the catalyst in close proximity of the targeted C-H bond. This type of metalation can be directed via either a Lewis basic directing group of the substrate such as heteroatoms or unsaturated bonds (Scheme **1.3a**) or by oxidative addition into a carbon-(pseudo)halide bond (Scheme **1.3b**).[14]



Scheme 1.3: Different strategies for C-H functionalisation.

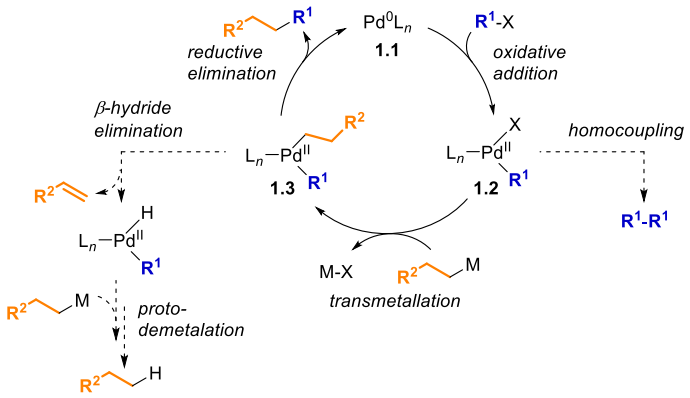
A different approach consists in the remote functionalisation of alkyl C-H bonds. Originally developed for controlling polymer topology,[20–23] olefin isomerisation as a vehicle to enable functionalisation at a distant site has recently gained increased attention (Scheme **1.3c**).[24–28] The progression of a transition metal catalyst along an alkyl chain via dynamic displacement, termed "chain-walking", is often associated with the translocation of a double-bond to a terminal position, presumably due to steric effects, or to a resonance-stabilised position such as adjacent to an aromatic moiety or functional group. Besides allowing the formal functionalisation of C-H bonds, it can also serve as a regioconvergent instrument by transforming e.g. a regioisomeric mixture of *E*- or *Z*-alkenes selectively to one sole product. Thus, various different catalytic systems have already been successfully developed with different transition metals such as zirconium, cobalt, nickel, ruthenium and palladium.[24–28]

The evolution of synthetic organic chemistry follows a clear path towards improved efficiency of the overall transformation.[3–5] Moreover, the newly developed methods further expand the synthetic toolbox enabling the synthesis of increased complexity. In the next part, we will discuss the development of palladium-catalysed cross-coupling with alkylboron reagents as well as the development of intentional palladium-catalysed migratory functionalisation, the two core-subjects of this thesis. Consequently, the other transition metals used for these types of transformations will not be discussed for the sake of conciseness.

1.2. Palladium-Catalysed Suzuki-Miyaura Cross-Coupling with Alkylboron Reagents

1.2.1. Introduction

In virtue of broad functional group tolerance, operational simplicity, environmental benign nature and thermal stability of the transmetalation agents, the Suzuki-Miyaura cross-coupling reaction (SMC) has emerged as a powerful synthetic tool.[29,30] Notably, the *B*-alkyl adaptation has become one of the most popular cross-coupling protocol since the first report in 1986 of the cross-coupling reaction between alkylboron reagents and aryl or alkenyl halides.[7,31–34] Furthermore, the wide application of organoboron compounds since more than 60 years in organic synthesis provides a multitude of methods and ease of preparation and handling as well as commercial availability of a multitude of different organoboron reagents.[35,36] However, the development of C(sp^3)-organometallics in cross-coupling reactions has been more challenging than the related C(sp^2)-couplings due to several limitations. Some of these issues are the spontaneous decomposition of alkyl organometallics via β-elimination or proto-demetalation,[37] and the preparation of the organometallic reagents without purification as they are often not air-stable, translating to superstoichiometric amounts of organometallics used. Moreover, compared to their C(sp^2)-analogues, the three organometallic processes (oxidative addition, transmetalation, reductive elimination) become more critical due to the slower respective rates, hence opening new pathways for side-reactions (Scheme **1.4**) and thereby sometimes requiring various additives.[38–41]



Scheme 1.4: Mechanistic features of palladium-catalysed cross-coupling with alkyl-organometallics.

1.2.2. Mechanistic Aspects of the Suzuki-Miyaura Cross-Coupling Reaction

The mechanism of oxidative addition[42–47] and reductive elimination[48–53] have been thoroughly studied and are now relatively well understood. However, there has been a dichotomy of opinion about the transmetalation event in SMC, complicated by the wide range of different organoboron reagents (Figure **1.1**) and an ever-increasing portfolio of ligands, electrophiles, bases, additives and solvent systems.

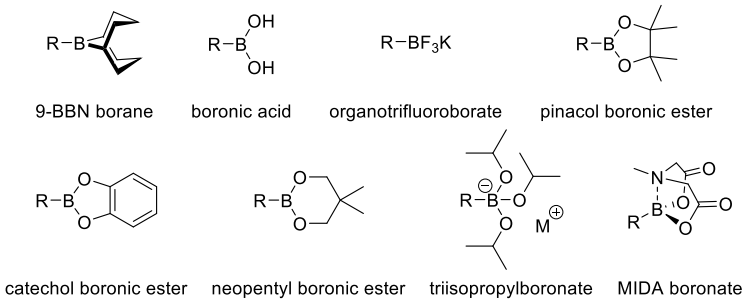
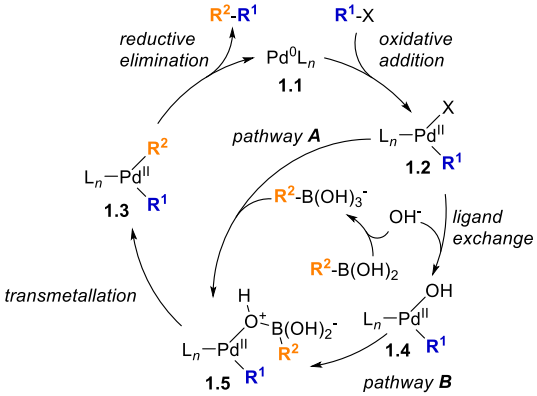


Figure 1.1: Selected examples of popular boron coupling partners.

The complexity during the transmetalation event arises from the fundamental properties of boron-species. Association of a fourth ligand to the Lewis acidic three-coordinated boronic species to generate an "ate" complex (**1.5**, Scheme **1.5**) is required to enable efficient transfer of the organic moiety to palladium. The provenance of this fourth ligand is where the opinions differ and two distinct pathways are considered. In the so-called "boronate" pathway (pathway **A**, Scheme **1.5**) a four-coordinate boronate species is preformed, or generated *in situ* through an equilibrium, which then associates with intermediate **1.2** of the oxidative addition to form intermediate **1.5**. Alternatively, a hydroxy-palladium intermediate **1.4** is obtained after ligand exchange, which then acts as a Lewis base toward a three-coordinate boron species, thus only generating intermediate **1.5** upon association with the palladium complex **1.4**, the so-called "oxo-palladium" pathway (pathway **B**, Scheme **1.5**).[54,55]



Scheme 1.5: Simplified generic mechanism for SMC of a boronic acid with an organohalide.

1.2.2.1. Mechanistic studies on the transmetalation of C(sp^2)-boron species

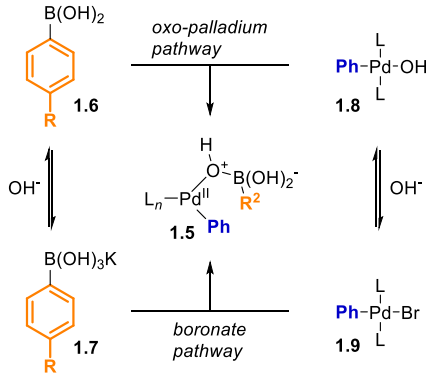
Several density functional theory (DFT) calculations on different aspects of SMC were reported by assuming that the transmetalation proceeds through pathway **A**.[56–59] Only Maseras and co-workers directly compared both pathways **A** and **B**.[60–64] Despite similar or even lower energetic barrier for the oxo-palladium pathway (**B**), they could not locate the transition state for the necessary displacement of the halide with hydroxide at palladium. Thus, they concluded that the boronate pathway (**A**) is responsible for the formation of the common intermediate **1.5** because of lack of ready access to the hydroxy-palladium intermediate **1.4**. Additionally, the boronate species as well as the palladium-halide complex have both been detected in the reaction mixture by ESI-MS,[65–67] but not the hydroxy-palladium complex. However, the presence of intermediates does not reveal their reactivity characteristics.

Instinctively, the isolation of preformed boronate species such as trihydroxyboronate salts[68,69] or trialkoxyboronate salts[70–72] and subsequent engagement in base-free SMC was further believed to be evidence for the boronate pathway. However, their solubility in the coupling-medium is low, and thus it is unclear whether there is an equilibrium during the catalytic flux constantly replenishing base and boronic acid/ester in the reaction medium or not.

A HPLC-derived kinetic study by Smith[73] indicated that the rate-limiting step with aryl bromide is the oxidative addition, whereas with aryl iodide it is post-oxidative addition. Further kinetic modelling of the proposed [$L_2PdX(Ar)$] intermediates (X = Br, I) suggested similar reactivity toward transmetalation of both halide complexes. Thus, it was interpreted as evidence against the oxo-palladium pathway in which halide substitution precedes transmetalation. Furthermore, the reaction failed when bicarbonate was used as base. Typical pK_a values of aryl boronic acid (8.8) relative to carbonate (10.3) and bicarbonate (6.4) was taken as evidence for the formation of boronate species, an essential step for the boronate pathway.

However, it was noted by Miyaura in 2002 that a hydroxy-palladium complex [$(Ph_3P)Pd(OH)(Ph)]_2$ reacts at room temperature with *p*-anisylboronic acid to give homo- and cross-coupling products in 85% yield, thus demonstrating the possibility of the second step in

the oxo-palladium pathway.[74] Further kinetic studies on stoichiometric reactions from the groups of Amatore and Jutand,[51] Hartwig[75] and Schmidt[76] provided compelling and conclusive evidence that the oxo-palladium pathway is kinetically most favourable, at least for the systems tested therein. Amatore and Jutand[51] studied various transmetalation scenarios with electrochemical techniques combined with heteronuclear NMR spectroscopy. Their findings indicated a very slow transmetalation rate for the boronate **1.7** with the halide complex **1.9** (Scheme **1.6**). Additionally, halide complex **1.9** was found to be in a rapid equilibria with the hydroxy-palladium complex **1.8**, which is in direct contrast with the DFT calculations,[60–63] and then underwent transmetalation efficiently with the boronic acid **1.6**. The authors were also able to rule out two alternative transmetalation pathways (**1.6** + **1.9** and **1.7** + **1.8**).



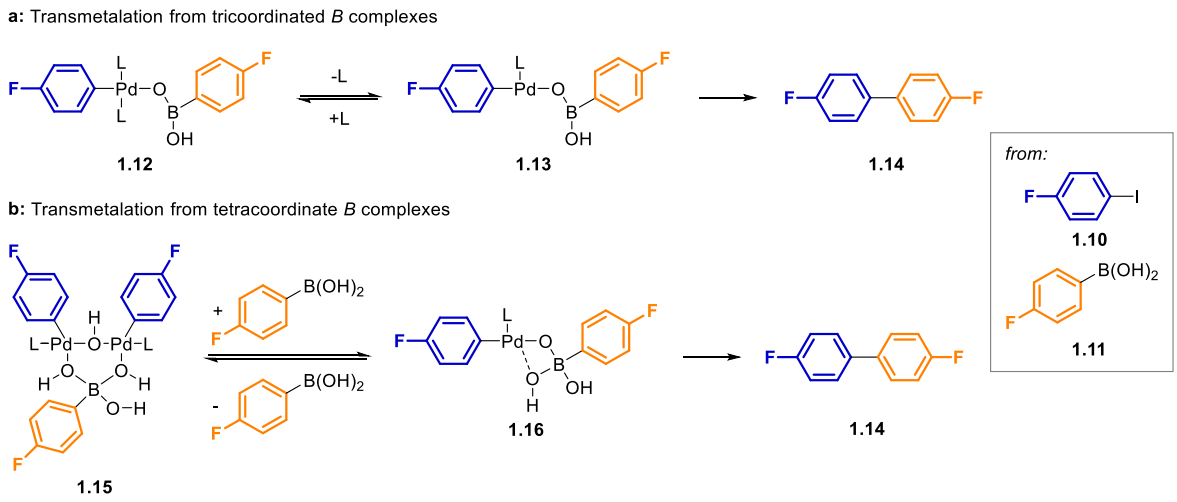
Scheme 1.6: Different equilibria for the possible species prior to transmetalation in SMC.

Hartwig[75] employed ^{31}P-NMR spectroscopy to measure the rate of the stoichiometric transmetalation of the halide complex **1.9** with an aryl trihydroxyboronate **1.7** (boronate pathway) as well as of an in situ generated hydroxy-palladium complex **1.8** with an aryl boronic acid **1.6** (oxo-palladium pathway). The latter was found to be four orders of magnitude faster than the prior was. Besides this, they also showed that the populations of palladium halide complex **1.9** and hydroxy-palladium complex **1.8** are similar to each other as well as the population of boronic acid **1.6** and trihydroxyboronate **1.7** in the presence of water and carbonate bases. It is noteworthy however, that these studies were conducted in the presence of 18-crown-6, thus attenuating the availability of K^+ counterion to **1.7** for halide abstraction from Pd in **1.9**, and thus impacting its rate. Schmidt[76] further compared the rate of stoichiometric homocoupling of phenyl boronic acid by UV analysis under phosphine-free conditions. The formation of biphenyl proceeding through two-fold transmetalation was found to occur about two times faster when the boronic acid **1.6** was added to an equilibrium mixture of $[Pd^{II}(OAc)_2]$ and NaOAc, than the addition of $[Pd^{II}(OAc)_2]$ to an equilibrium mixture of **1.6** and NaOAc, thus excluding the involvement of a trihydroxyboronate.

Interestingly, much less controversy exists about the existence of the putative pre-transmetalation intermediate **1.5** (Scheme **1.5**), even though it was never observed or characterised by chemists until only recently. Realistically, because of a computationally predicted barrier value of 14-22 kcal mol^{-1},[54] special techniques are required to elucidate the

structure of **1.5**. One such technique is rapid injection NMR (RI-NMR),[77] which was further developed by the group of Denmark.[78]

With this technique, Denmark was able to detect and characterize different Pd-O-B complexes (**1.12, 1.15, 1.16**, Scheme **1.7**).[79,80] During their studies, they made several important discoveries. The synthesis of the tricoordinate *B* complex **1.12** proceeded quantitatively when prepared from a hydroxy-palladium complex and an arylboronic acid, but yielded only 10% when prepared with a palladium-halide complex and an aryl boronate. However, the formation of **1.12** must proceed through a tetracoordinate *B* intermediate such as **1.16**, which is formed initially, succeeded by rapid loss of a molecule of water. Further investigations with a mono-ligated arylpalladium hydroxy complex lead to a new bridged *bis*-arylpalladium arylboronate complex **1.15**, which upon further addition of arylboronic acid **1.11** yielded the tetracoordinate *B* complex **1.16**. Kinetic studies of the transfer of the aryl group from boron to palladium showed that *B* complex **1.15** is first converted to *B* complex **1.16** prior to transmetalation. Moreover, an inverse dependence of phosphine ligand for the transmetalation of tricoordinate *B* complex **1.12** supports that a dissociation of a phosphine ligand is a pre-equilibrium process that leads to the hypothetical 14-electron palladium complex **1.13**.

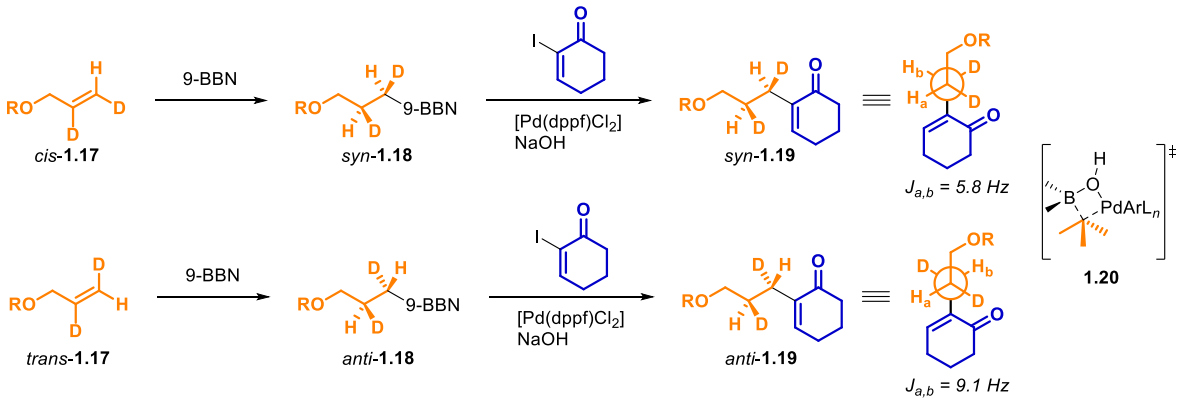


Scheme 1.7: Transmetalation pathways for three different pre-transmetalation Pd-O-B intermediates.

Hence, for the first time, competent pre-transmetalation species containing Pd-O-B linkages that undergo SMC were identified and characterised. However, the observation of transmetalation from a tricoordinate boron centre challenges the current belief of boron activation by base prior to transmetalation.[79,80] Further investigations revealed two competing factors which are crucial for transmetalation to happen.[81] First, the ability to access a coordinatively unsaturated palladium centre, and second the nucleophilic character of the B-*ipso* carbon. In this study, they also observed faster transmetalation rate for catechol- and glycol arylboronic ester compared to the arylboronic acid, and they demonstrated that glycol arylboronic ester reacts under anhydrous catalytic conditions, indicating that a prior hydrolysis step is not required, raising further questions.

1.2.2.2. Mechanistic studies on the transmetalation of C(sp^3)-boron species

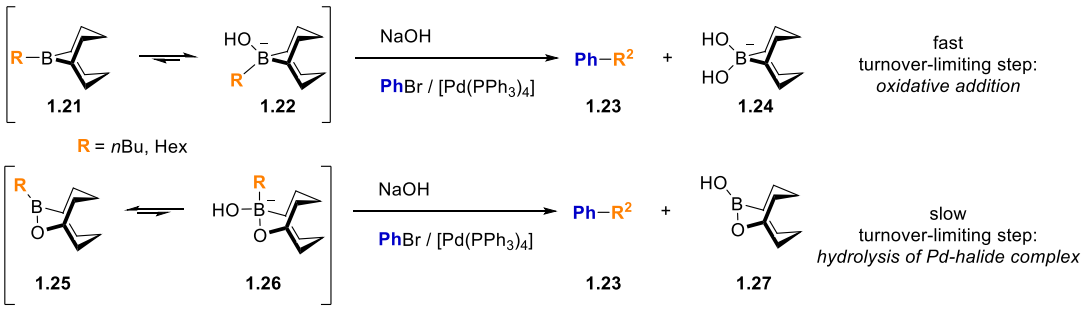
Whereas several mechanistic studies have attempted to determine the pathway of the transmetalation of C(sp^2)-boron species, only a few studies have addressed the C(sp^3) analogues. Additionally to the dichotomy between the two pathways, transmetalation of C(sp^3)-centres may also have different stereochemical consequences due to two possible S_E2 mechanism (retentive or invertive) if a *secondary* or *tertiary* alkylboron nucleophile is used.[82,83] Woerpel[84] and Soderquist[85] in back to back reports independently studied the stereochemical outcome of such a transmetalation with deuterium labelling. Woerpel demonstrated that diastereomeric dideuterioalkenes *cis*-**1.17** and *trans*-**1.17** underwent hydroboration to the corresponding alkylboranes **1.18** followed by SMC with α-iodocyclohexenone. The *syn*-**1.19** coupling product was obtained from the *cis*-**1.17** alkene, and the *anti*-**1.19** coupling product from the *trans*-**1.17** alkene respectively, as confirmed by ^{1}H-NMR analysis of the coupling constants ($J_{a,b}$ = 5.8 Hz for *syn*-**1.19**, $J_{a,b}$ = 9.1 Hz for *anti*-**1.19**). Thus, it was concluded that the transmetalation in *B*-alkyl SMC proceed through retention of configuration as the hydroboration is a *syn*-addition process. This was in agreement with Soderquist findings, in which he additionally proposed a four-membered cyclic transition state **1.20**.[85]



Scheme 1.8: Stereochemistry of the transmetalation of alkylboranes.

Soderquist further conducted systematic studies on the transmetalation step for the coupling of primary alkylboranes **1.21** and alkylborinates **1.25** with bromobenzene and NaOH (Scheme **1.9**). According to ^{11}B-NMR, the Lewis acidic alkylborane **1.21** readily forms the boronate complex **1.22** in presence of the base. The kinetics of the coupling with PhBr were found to be first-order in electrophile, and pseudo-zero-order in both alkylboron **1.21** and base. In contrast, no hydroxyborinate complex **1.26** was formed in the presence of base, and kinetics were found to be pseudo-zero-order in both PhBr and alkylborinate **1.25**, but first-order in NaOH. Moreover, competitive studies demonstrated that when both species are present, only alkylboranes **1.21** undergo coupling. Additional difference between the two organoboron species was found during stoichiometric study of required NaOH. Alkylboranes **1.21** necessitate two equivalents to perform efficiently, whereas SMC with alkylborinates **1.25** still proceeds efficiently with just one equivalent. With these data, it was concluded that

alkylboranes **1.21** proceed through the boronate pathway, and alkylborinates **1.25** through the oxo-palladium pathway.



Scheme 1.9: Pathways for the transmetalation of alkylboranes.

Since then several reports on stereospecific Pd-catalysed SMC employing directing groups were reported.[86–88] Several of them, however, proceeded under inversion of the stereocentre. Suginome further demonstrated that the addition of a Lewis acid could completely reverse the pathway of transmetalation from invertive to retentive.[83] Interestingly, Biscoe observed that the non-directed SMC of unactivated *sec*-alkylboron (**1.30**, Scheme **1.10**) with a mono-ligated palladium catalyst [PdP(*t*Bu)$_3$] proceeds with inversion of configuration,[89] which is in direct contrast to the comparable findings of Woerpel[84] and Soderquist.[85]

To better understand the parameters influencing the mechanism of transmetalation he teamed-up with Sigman to conduct a mechanistic study using predictive statistical models.[90] They demonstrated, that the outputs could be expressed in two readily interpretable terms that discriminate between the two S_E2 pathways (Figure **1.2**): the π-back bonding represented by the average energy of the P-C antibonding orbitals, and the ligand's σ-donation capability represented by the energy of the lone pair orbital of phosphorous. Their results suggest that π-back bonding may stabilise the coordination of a π-donor ligand X (e.g. OH^-) to Pd, and thus favouring a retentive mechanism **1.28**. Whereas strong σ-donation from the ligand may stabilise a two-coordinate, cationic palladium complex and thus favouring an invertive mechanism **1.29**. A correlation between the enantiopurity of the product **1.32** (Scheme **1.10**) and the branched:linear ratio further revealed that the β-hydride elimination is responsible for both racemisation and isomerisation to the linear product. They also observed a modest trend relating the steric bulk with the branched:linear ratio, which is also consistent with the reports of large ligands facilitating reductive elimination over β-hydride elimination.[33]

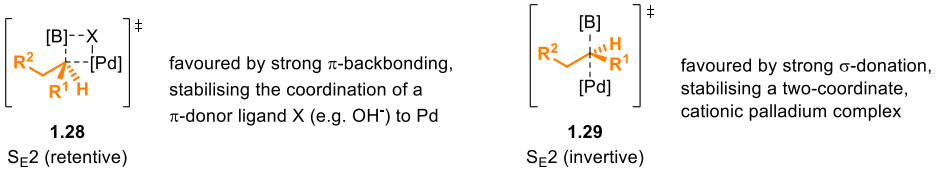
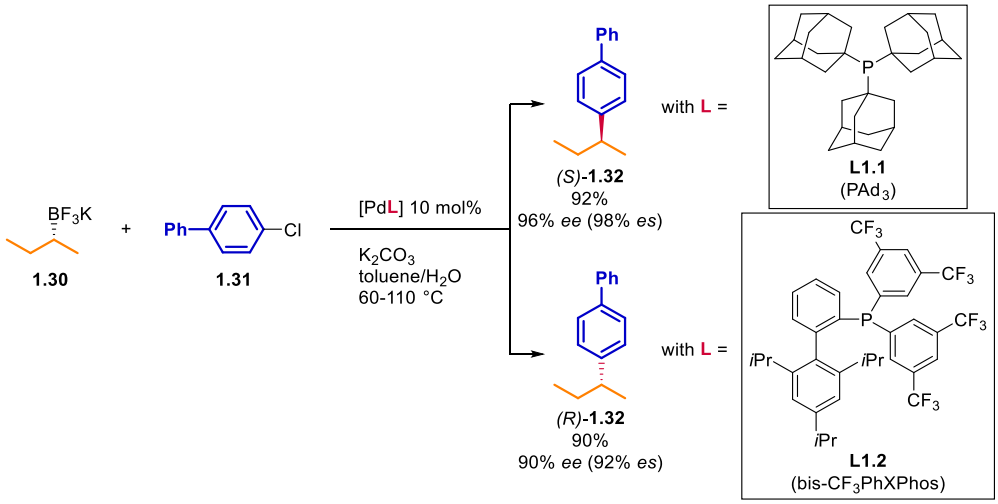


Figure 1.2: Electronic factors influencing the mechanism of transmetalation of *secondary* alkylboron nucleophiles.

The outcome of this study of Biscoe and Sigman suggested that both enantiomers of a cross-coupling product could be selectively accessed through the use of a single enantioenriched alkylboron nucleophile with the proper selection of the phosphine ligand. They identified the strongly σ-donating ligand PAd_3 (**L1.1**) to promote the stereoinvertive pathway furnishing among others (*S*)-**1.32** in excellent yield and stereoinversion. Whereas strongly π-accepting ligand bis-CF_3PhXPhos **L1.2** promoted the stereoretentive pathway furnishing among others (*R*)-**1.32** in excellent yield and stereoretention (Scheme **1.10**).

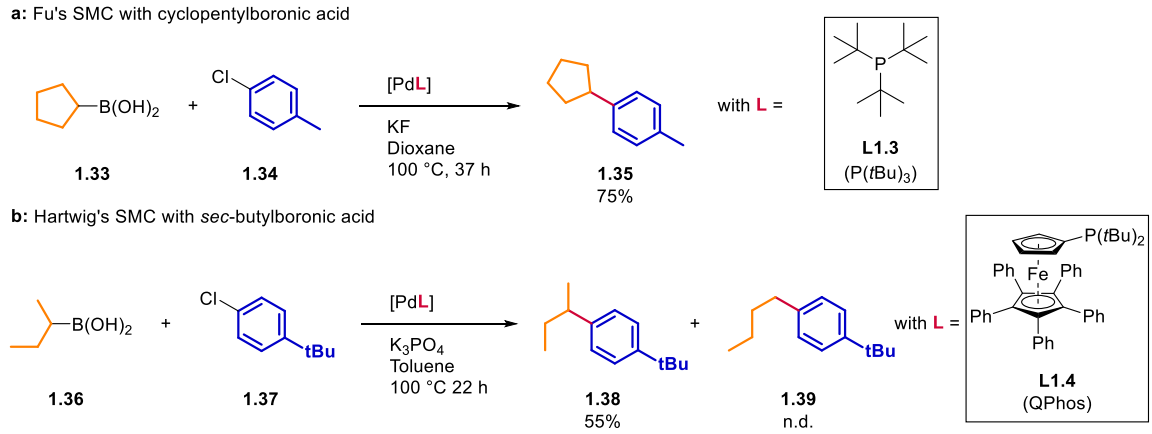


Scheme 1.10: Enantiodivergent SMC using enantioenriched alkylboron nucleophiles.

1.2.3. Challenges in Suzuki-Miyaura Cross-Coupling with Alkylboron Nucleophiles

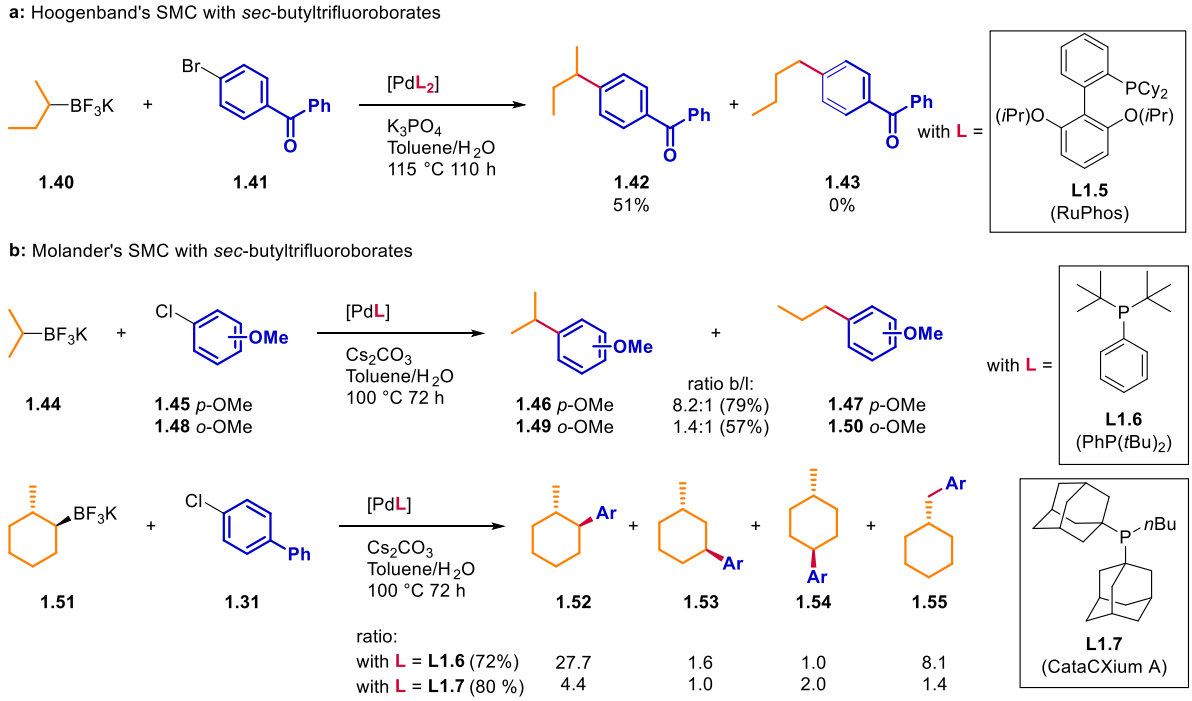
Most of the developments and applications of the *B*-alkyl SMC have been conducted on alkylboranes such as 9-BBN boranes (Figure **1.1**) or related, and a broad range of *primary* alkyl moieties were cross-coupled with either C(sp^2)- or C(sp^3)-electrophiles.[7,32–34,91] Interestingly, the boronic acid analogues have witnessed a far minor development despite their superior stability and availability. This is due to the fact that their use is bound to slower transmetalation rates and side reactions such as protodeboration.[6] A way to overcome this issue is to use trifluoroborate salts (Figure **1.1**), as they slowly release boronic acid into the reaction mixture, hence minimising the concentration of boronic acid and radically slowing down the protodeboration. By exploiting this strategy, Molander developed various *primary* alkyl trifluoroborate reagents which undergo efficient SMC.[92,93]

Further challenges arise when moving from *primary* to *secondary* or *tertiary* alkylborane species, as the notoriously difficult to suppress β-hydride elimination becomes a possible side-reaction. Additionally, the transmetalation becomes even slower due to steric hindrance. Fu and Hartwig were the first to report the successful SMC of *secondary* alkylboronic acid (Scheme **1.11**).[94,95] Although, they each reported only one example, and considerable amount of isomerised product **1.39** was obtained together with the direct SMC product **1.38** when *sec*-butylboronic acid **1.36** was employed.



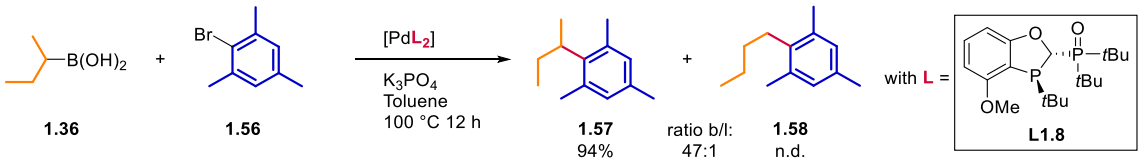
Scheme 1.11: Seminal examples of SMC with *secondary* alkylboronic acids.

Hoogenband and Molander then independently developed the more general SMC of *secondary* alkyltrifluoroborates (Scheme **1.12a**).[96,97] It's noteworthy to mention that no isomerisation to the linear product **1.43** was observed when Hoogenband employed *sec*-butyltrifluoroborate **1.40**, but only modest yields were obtained.[96] Molander's system provided higher reactivity, but considerable amounts of isomerised SMC product due to β-hydride elimination was observed in sterically hindered systems (Scheme **1.12b**).



Scheme 1.12: SMC with *secondary* alkyltrifluoroborates.

Additionally to the work of Biscoe and Sigman (Scheme **1.10**),[89,90] Tang reported a general method for the SMC alkylboronic acids with hindered aryl bromides and triflates furnishing the desired product in excellent yield and branched/linear ratio with their newly developed P,P=O ligand **L1.8** (Scheme **1.13**).[98,99]



1.36 **1.56** **1.57** 94% ratio b/l: 47:1 **1.58** n.d.

Scheme 1.13: General SMC with *secondary* alkylboronic acids.

A different approach to achieve selective SMC of *sec*-alkylboron species is achieved by using directing groups which chelate to the catalyst, or by using α-anion stabilising substituents such as an additional boron atom or a position adjacent to functional groups,[6,100] but their description is outside the scope if this introduction.

1.2.4. Conclusion

The SMC is one of the few reactions that have been applied in organic synthesis ranging from fundamental research to large-scale manufacturing processes, and is doubtless an essential tool in the chemist's toolbox. The advantages over other cross-couplings are clear. The organoboron species are accessible through various paths and generally exhibit stability to air, moisture and heat. Furthermore, the SMC generally employs mild reaction conditions and therefore tolerates various functional groups, and generates nontoxic boron by-products.

In-depth mechanistic studies have demonstrated without doubt the existence of two transmetalation pathways, depending on the organoboron species and reaction conditions used. Recent studies on the pre-transmetalation intermediates further demonstrated the impact that a single reaction parameter, such as the amount and nature of ligand or the presence of water, can have. Moreover, due to constantly changing reaction conditions due to the release of boric acid ($B(OH)_3$) and consumption of base it is possible that both the oxo-palladium and the boronate pathways compete during different stages of the SMC.

Whereas the *B*-alykl SMC has become a mature and popular tool for *primary* alkylboranes, the adaptation to the *secondary* or *tertiary* analogues remains scarce due to competing side-reactions.

1.3. Palladium-Catalysed Site-Selective Migratory Functionalisation

1.3.1. Introduction

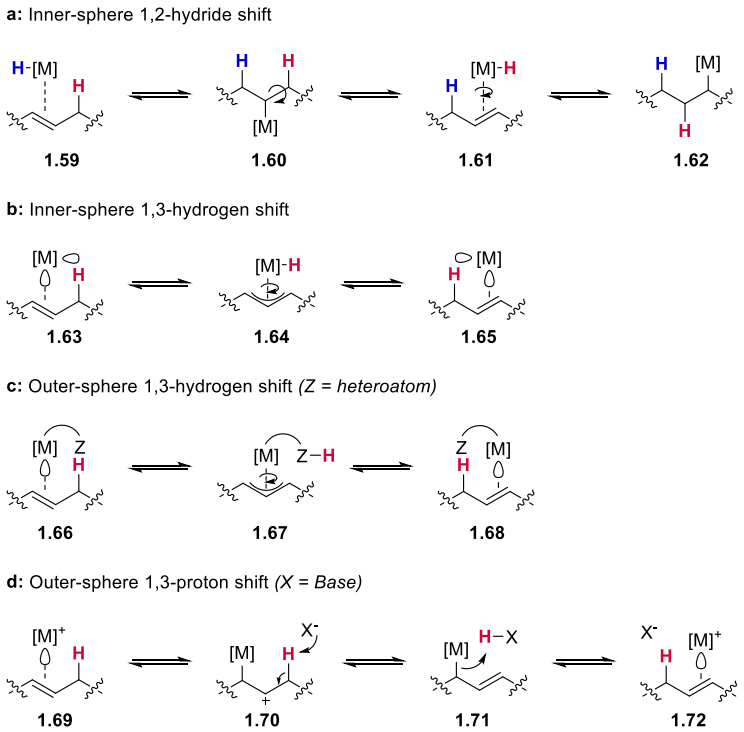
The remote functionalisation through initial interaction at a functionalised site leading to the selective activation of an unreactive C-H or C-C bond at a distal position remains one of the biggest challenges in organic chemistry with enormous potential. Many advances were made by the use of tethers placing a transition metal-catalyst proximal to the reaction site, but they often have the drawback of employing high molecular weight linkers.[12–19] Thus, the remote functionalisation through transition metal-catalysed chain-walking has been gaining increased attention in the last decade and a variety of catalytic systems have been developed.[24–28] However, transition-metal complexes are known to isomerise double bonds along an alkyl

chain in a statistical manner, therefore it can only be directed if associated with a strongly favoured termination step.[101]

1.3.2. General Mechanistic Aspects

Olefin isomerisation can proceed through either 1,2- or 1,3-hydrogen shift mechanisms, and both pathways can potentially compete with each other.[102,103] In the Inner-sphere 1,2-hydride shift (Scheme **1.14a**), the metal-hydride complex **1.59** undergoes hydrometalation with the olefin to furnish the well-defined alkyl-metal species **1.60**. Subsequent β-hydride elimination gives the isomerised olefin π-complex **1.61**, which after rotation and hydrometalation gives the isomerised alkyl-metal species **1.62**. This process generally leads, after several repetition along an alkyl-chain, to the formation of the thermodynamically more stable primary organometallic species.[104]

The 1,3-hydride shift can proceed through either an inner-sphere or outer-sphere mechanism. The inner-sphere mechanism (Scheme **1.14b**) requires coordinatively unsaturated organometallic species possessing two vacant valence orbitals (14 electron species). Oxidative addition of the metal to the C-H bond facilitated by agostic interaction of the allylic hydrogen and the vacant metal-orbital (**1.63**) yields a η^3-allyl metal-hydride intermediate **1.64**. This intermediate gives, after rotation and reinsertion of the hydride, the isomerised olefin **1.65**. The regiochemistry can vary and depends on the temperature and the nature of the catalyst and ligands.[105] Alternatively, the outer-sphere mechanism (Scheme **1.14c**) can proceed if the ligand acts as a base, enabling, after complexation (**1.66**) the deprotonation to form the π-allyl metal complex **1.67** and reprotonation to provide the isomerised olefin **1.68**.[106]



Scheme 1.14: General mechanism for the transition metal-mediated olefin isomerisation.

Finally, the outer-sphere 1,3-proton shift mechanism can occur with the assistance of a base in case of π-acidic transition complex such as cationic palladium or silver complexes. The alkyl metal carbonium species **1.69** sufficiently acidifies the allylic proton to enable intermolecular deprotonation furnishing the allyl intermediate **1.71**. Subsequent protonation cleaves the metal-carbon bond and furnishes the isomerised olefin **1.72**.[107–109]

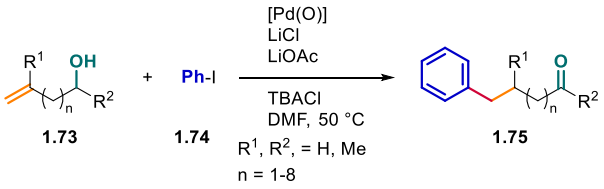
However, palladium catalysed migratory remote functionalisation has been found to proceed in most cases through a non-dissociative inner-sphere 1,2-hydride shift, enabling the migration through *tertiary* stereocentres with retention of configuration, and initial chemoselectivity between different olefin moieties.[27]

1.3.3. Key Developments

Various different initiation and termination processes for palladium-catalysed remote functionalisation through chain-walk have already been described despite the short development period.

1.3.3.1. Redox-Relay Remote Functionalisation Involving Chain-Walking

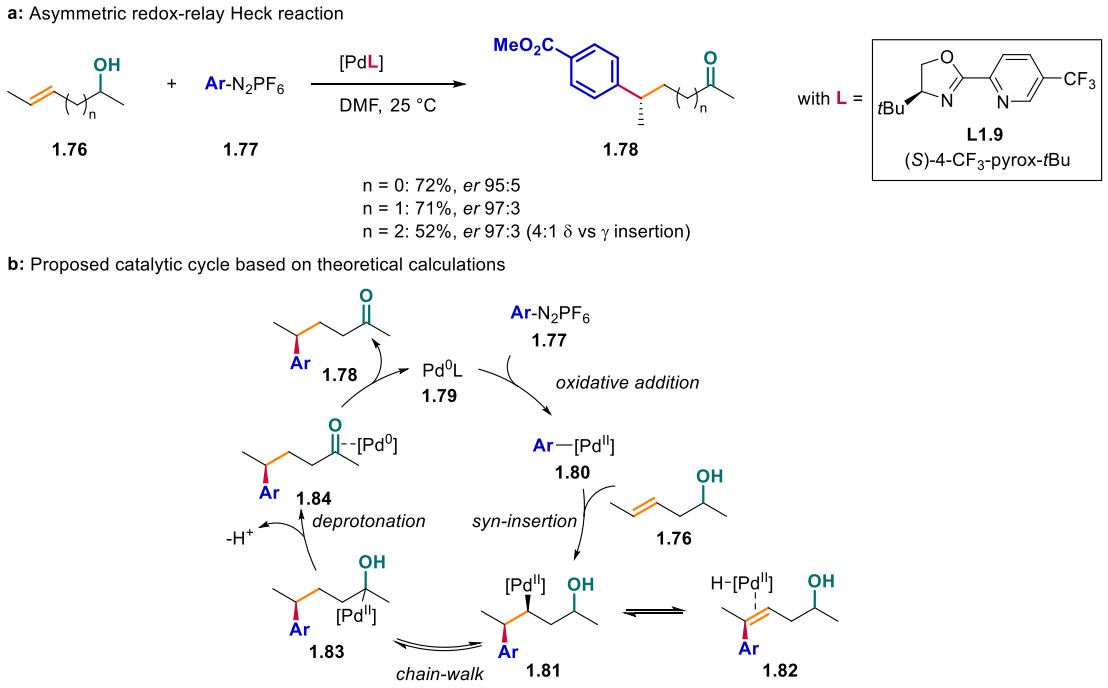
The first report of a redox-relay Mizoroki-Heck reaction was disclosed in 1976 by Heck, in which allyl- and homoallyl alcohols underwent arylation and subsequent chain-walk until captured by the alcohol function to give a carbonyl compound.[110] Shortly thereafter, Chalk reported a similar approach with unsaturated alcohols.[111,112] It is noteworthy to mention that a product containing an aldehyde was observed when 9-decen-1-ol was engaged with iodobenzene in the reaction, indicating the ability of the palladium-catalyst to undergo long-range chain-walk. However, the approach described in these seminal reports provided low yields of a mixture of products under harsh conditions. These early examples were then generalized and extended to the remote functionalisation of longer-chain olefinic alcohols **1.73** to yield the corresponding carbonyls **1.75** by Larock in 1989 (Scheme **1.15**).[113] This approach has, since then, found application in several reports.[114–120]



Scheme 1.15: Seminal reports on the redox-relay Heck reaction.

Sigman disclosed in 2012 the asymmetric remote functionalisation of allyl- homoallyl- and bis-homoallyl alcohols **1.76** using a chiral PyrOx ligand **L1.9** and aryldiazonium salts **1.77** as substrates (Scheme **1.16a**).[121] Various ketones and aldehydes products were obtained in high yield and excellent stereoselectivity. Importantly, since then, asymmetric Heck reactions have been thoroughly investigated, but are generally limited to cyclic alkenes or those creating quaternary carbons stereocentres to prevent β-hydride elimination responsible for racemisation.[122] Thus, styrene formation and alkene dissociation from the catalyst must be

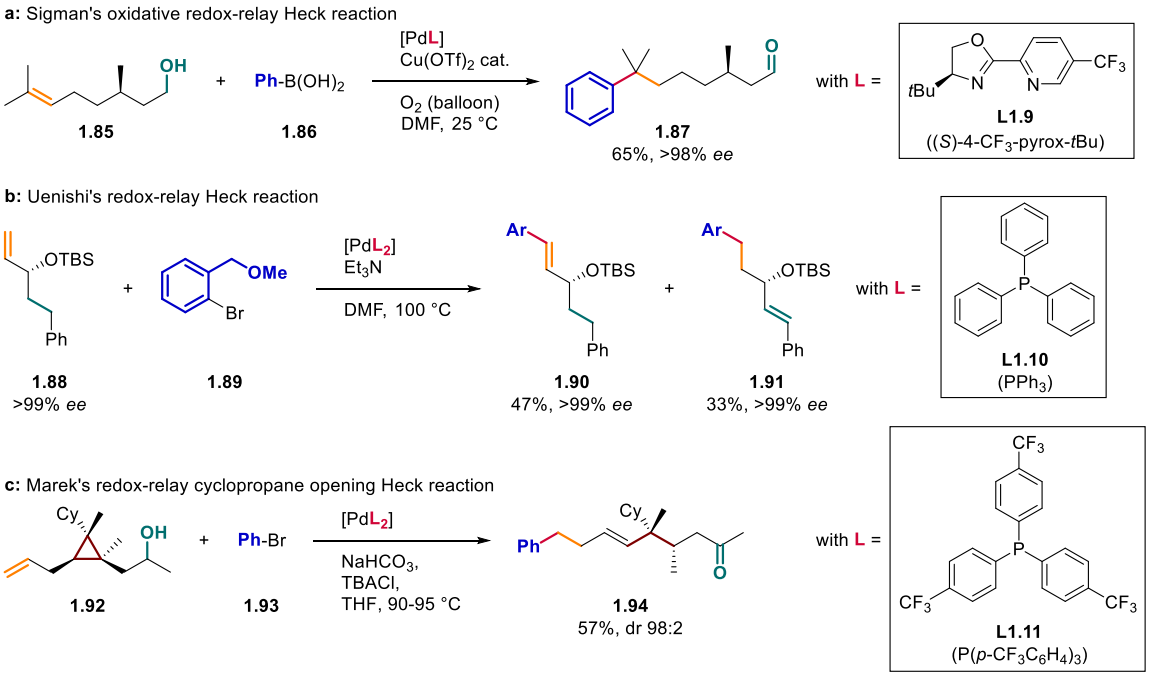
avoided for an enantioselective Heck type reaction. Theoretical studies on the mechanism of the asymmetric redox-relay Heck reaction (Scheme **1.16b**) indicated a possible, but disfavoured β-hydride elimination at the newly created stereocentre **1.82**. Instead, the palladium catalyst can move back and forth on the alkyl chain without dissociating from the alkene intermediates until eventual migration to the thermodynamically stable α-position of the hydroxyl group **1.83**. Deprotonation then leads to the carbonyl compound **1.78** and regeneration of the catalyst **1.79**.[123,124]



Scheme 1.16: Asymmetric redox-relay Heck reaction and proposed catalytic cycle thereof.

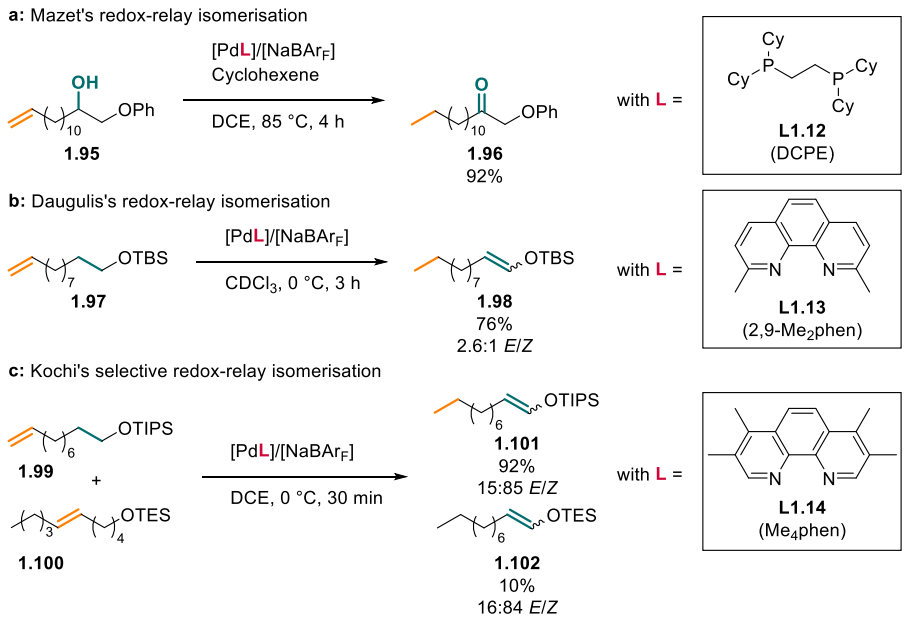
This methodology was then further applied to alkenyl triflates[125–127] and alkynyl iodanes[128] as well as to the alkenylation of acyclic enol ethers[129] and to the remote styrene formation as terminating step.[130] It should also be noted that all-carbon quaternary stereocentres are obtainable when tri-substituted alkenes are engaged. Significant extension was also achieved with the development of the redox-relay oxidative Heck reaction. Thus, arylboronic acids,[131–137] indoles derivatives,[138–140] carbamates[141] and phenols[142] were successfully engaged in oxidative redox-relay Heck reactions, which were also applied to enelactams[137,143] and alkenes possessing a remote carbonyl group providing α,β-unsaturated carbonyl compounds.[133]

Sigman and Uenishi independently demonstrated that *tertiary* carbon stereocentres are not racemised during a non-dissociative chain walking process (Scheme **1.17a**, **b**). [132,144] That occurs because the catalyst sticks to the same side of the alkene moiety newly generated through the β-hydride elimination, and thus the hydride atom cannot be transferred back to the original position from the opposite face. Additionally, Marek developed a redox-relay Heck reaction involving site-selective cyclopropane ring opening and isomerisation which provides the corresponding ketone product **1.94** maintaining the configuration at the stereogenic centres (Scheme **1.17c**).[145]



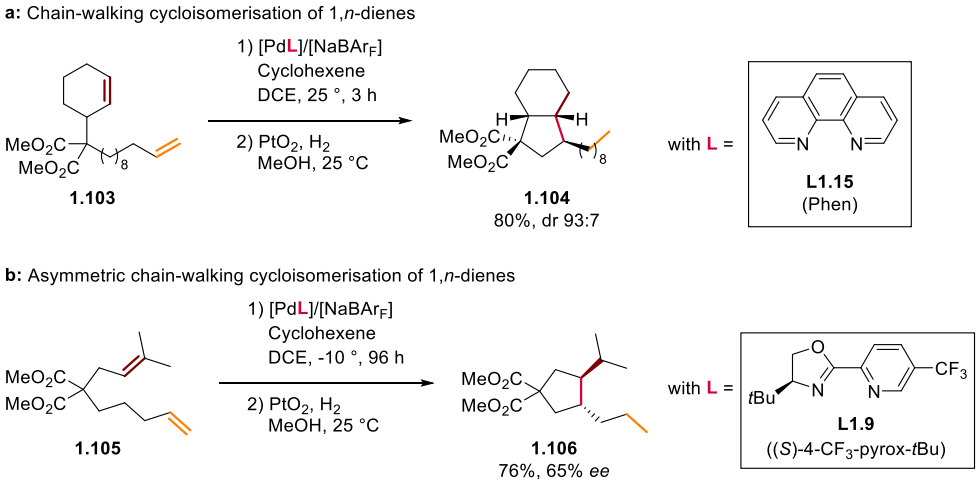
Scheme 1.17: Redox-relay Heck reaction of alkenyl alcohols containing a stereocentre on the alkyl chain.

Alternatively, an *in situ* generated palladium hydride can also be used to initiate the chain-walking, resulting in an overall redox-relay isomerisation of olefinic alcohols. In 2014 Mazet developed a methodology allowing the isomerisation of mono- to tetra substituted alkenyl alcohols (Scheme **1.18a**)[146] which he later also adapted to the deconjugative redox-relay isomerisation starting from α,β-unsaturated carbonyls.[147] Mazet then further combined these redox-relay isomerisation reactions with sequential multimetallic catalysis to enable subsequent functionalisation at the remote sites.[148,149] Daugulis reported in 2017 a redox-relay isomerisation from terminal alkenyl silyl ether to silyl enol ethers (Scheme **1.18b**).[150] Shortly thereafter, Kochi presented a very similar work, in which the selectivity for terminal **1.99** over internal alkenes **1.100** was additionally described (Scheme **1.18c**).[151]



Scheme 1.18: Redox-relay isomerisation of alkenyl alcohols and alkenyl silyl ethers.

Instead of relying on the formation of a carbonyl or a conjugated moiety as a terminating step, Kochi demonstrated in 2012 that if the substrate contains an additional strategically positioned alkene, a subsequent cyclisation of the palladium intermediate gives rise to various cyclopentane scaffolds (Scheme **1.19a**).[152,153] An asymmetric version was later published although with only modest enantioselectivity (Scheme **1.19b**).[154]



Scheme 1.19: Chain-walking cycloisomerisation of remote dienes.

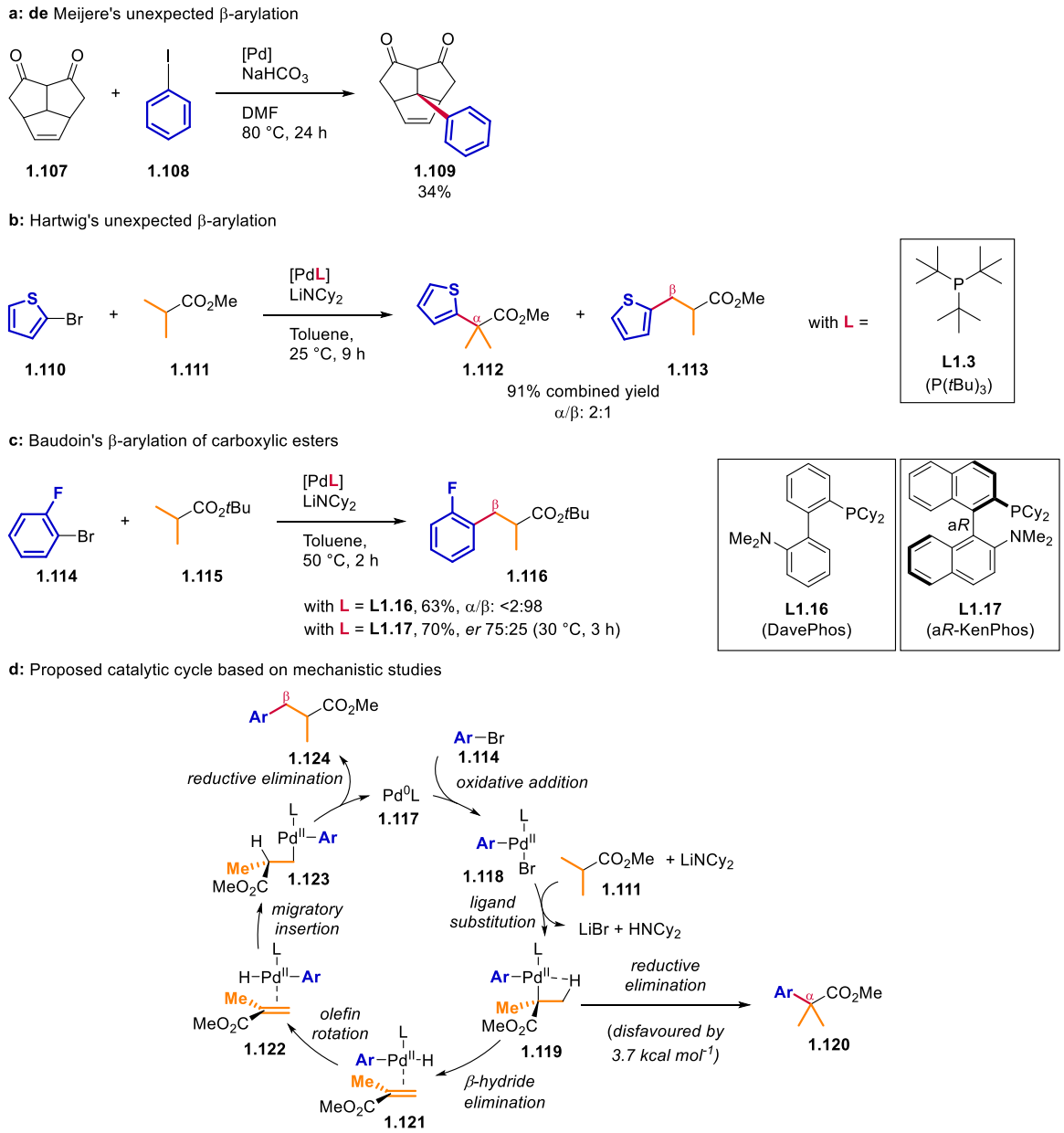
1.3.3.2. Remote Functionalisation through Chain-Walking enabled by Transient Alkenes

The propensity of a palladium-catalyst to undergo chain-walk along an alkyl chain during cross-coupling reactions has been generally considered as a side-reaction (*see also* Section **1.2.3**). However, if the metal migration can be stopped at a selective site by the reductive elimination event, a remote functionalisation through migratory cross-coupling reactions can be achieved.

In 1996 de Meijere reported the unexpected β-arylation on triquinanedione **1.107** (Scheme **1.20a**).[155] The authors initially proposed that the reaction proceeds through a dehydrogenation followed by a Heck reaction at to the newly formed double-bond. However, dehydrogenation of ketones normally requires stoichiometric amounts of $Pd(OAc)_2$, or a catalytic amount and stoichiometric reoxidant, but such conditions only led to the decomposition of the starting material (**1.107**). Furthermore, no side-product arising from the Heck reaction with the already present double-bond in **1.107** was observed. Thus, a migratory cross-coupling pathway through chain-walk could also be envisaged for this transformation. Hartwig discovered in 2002 that the coupling between methyl isobutyrate (**1.111**) and 2-bromothiophene (**1.110**) gave an unexpected 2:1 mixture of α- vs β-arylation products **1.112** and **1.113**, speculated to arise from reductive elimination of a palladium homoenolate obtained after rearrangement from the hindered palladium enolate (Scheme **1.20b**).[156]

In 2010 Baudoin reported a systematic study on the palladium-catalysed β-arylation reaction of carboxylic esters with aryl halides (Scheme **1.20c**).[157] Whereas a bulky phosphine ligand such as P(*t*Bu)$_3$ (**L1.3**) gave the direct coupling product, more flexible ligands such as DavePhos (**L1.16**) afforded mainly the β-arylated product **1.116**. Aryl halides bearing an *ortho* electron-withdrawing group or a heteroatom (O, S) at the adjacent position were necessary for

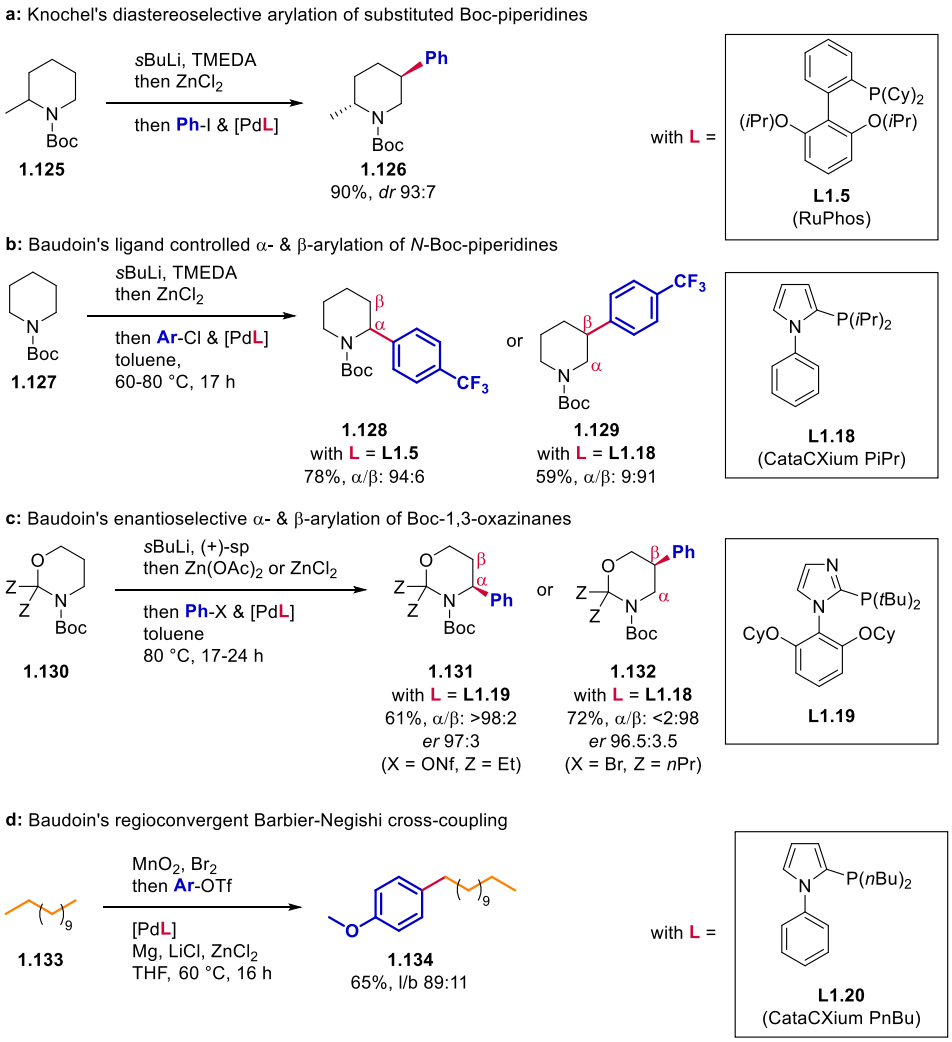
high-to-complete selectivity. The asymmetric version was also investigated, but only moderate enantioselectivities were obtained. An in-depth mechanistic study by Baudoin and Clot gave further insight in the selectivity resulting from the different ligands. A difference of ΔΔG# = 3.7 kcal mol^{-1} was found in favour of the β-arylation pathway over the reductive elimination leading to the α-arylated product with DavePhos **L1.16**, in presence of an *ortho*-fluoro-substituted aryl group **1.114** and methyl isobutyrate **1.111** (Scheme **1.20d**).[158] Baudoin then further developed this migratory cross-coupling reaction for the long-range arylation of dibenzyl-protected amino esters where a migration of up to 5 positions was demonstrated,[159] as well as for the β-arylation of silyl ketene acetals under milder conditions.[160]



Scheme 1.20: (Asymmetric) β-arylation of carboxylic esters through chain-walk.

In 2011 Knochel reported a study on the diastereoselective α-arylation of substituted *N*-Boc-piperidines via Negishi cross-coupling.[161] Unexpectedly, the β-arylation product **1.126** was obtained when the reaction was performed with 2-methyl-piperidine **.125** (Scheme **1.21a**). In

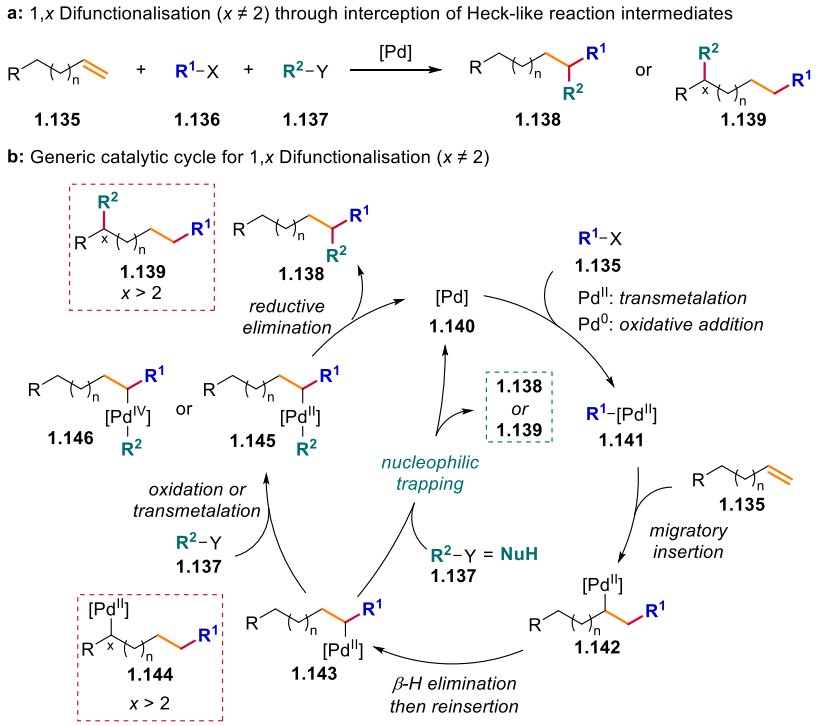
line with previous efforts to develop migratory cross-coupling reactions, Baudoin developed the ligand-controlled selective α- or β-arylation of *N*-Boc-piperidines **1.127** (Scheme **1.21b**),[162] which was then further extended to acyclic *N*-Boc amines,[163] and to the γ-selective arylation of allylic Boc-amines.[164] The selectivity was controlled by bulky and rigid phosphine ligands such as P(*t*Bu) (**L1.3**) or RuPhos (**L1.5**), which provided the direct α-arylated products, whereas more flexible *N*-phenylazole-based phosphine such as CataCXium PiPr (**L1.18**) gave mainly the β-arylated products. More recently the asymmetric version of this migratory Negishi cross-coupling was disclosed using an initial sparteine-mediated enantioselective lithiation of Boc-1,3-oxazinanes **1.130** (Scheme **1.21c**).[165] A broad range of alkenyl- and aryl-(pseudo-)halides were well tolerated and subsequent cleavage of the α- or β-arylated Boc-1,3-oxazinanes **1.131** & **1.132** gave β^2- and β^3-amino acids in good yields and excellent enantioselectivities. Baudoin also developed in 2016 a migratory Barbier-Negishi cross-coupling reaction for the long-range regioconvergent terminal functionalisation of mixtures of *secondary* alkyl bromides (Scheme **1.21d**).[166]



Scheme 1.21: Migratory Negishi-type cross-coupling reactions.

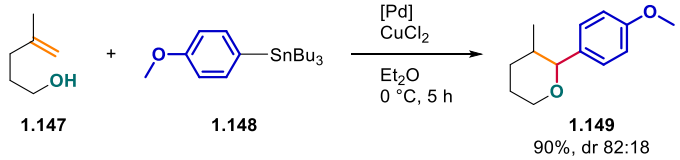
1.3.3.3. 1,*x*-Difunctionalisation (*x* ≠ 2) of Alkenes involving Chain-Walking

The interception of Heck-like reaction intermediates after chain-walk can also lead to interesting 1,*x*-difunctionalisation (*x* ≠ 2) of alkenes through migratory multicomponent cross-coupling (Scheme **1.22a**).[167] Such difunctionalisation can by initiated by either oxidative addition or transmetalation, depending on the substrate, followed by migratory insertion into the olefin. The obtained alkyl-metal species **1.142** then undergoes chain-walking to a stabilised position **1.143** or **1.144.** Subsequent oxidative addition or transmetalation followed by reductive elimination yields the 1,*x*-difunctionalised (*x* ≠ 2) product **1.138** or **1.139**. Alternatively, the alkyl-metal species can also be trapped by a nucleophile (Scheme **1.22b**).



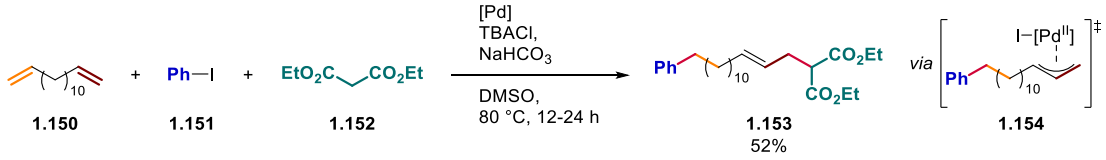
Scheme 1.22: 1,n-Difunctionalisation (n ≠ 2) through chain-walk.

In 1985 Yoshida disclosed the intramolecular 1,1-aryloxygenation of unsaturated alcohols (**1.147**) to afford substituted tetrahydropyrans (**1.149**, Scheme **1.23**),[168] followed by the related 1,1-aryloxygenation of unsaturated amines to afford 2-arylated pyrrolidines and piperidines.[169] Since then, significant developments have been made by combining different types of substrates. Thus various methods for the 1,1-arylhalogenation,[170–173] 1,1-aryloxygenation,[174–176] 1,1-diarylation,[177–184] 1,1-vinylarylation[185,186] as well as 1,1-arylboration[187,188] of alkenes involving chain-walking were disclosed.



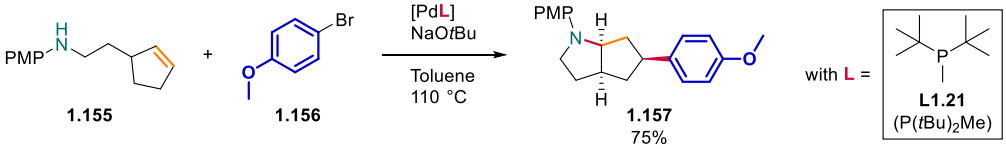
Scheme 1.23: Intramolecular 1,1-aryloxygenation of terminal alkenes.

In 1991 Larock reported a three-component coupling of aryl-iodides (**1.151**), non-conjugated dienes (**1.150**) and carbon nucleophiles (**1.152**) for the synthesis of 1,*x*-dicarbofunctionalisation (*x* ≠ 1,2) products **1.153** (Scheme **1.24**).[189] Mechanistically it was proposed that the chain-walking was driven by the formation of the stable π-allyl-Pd species **1.154**, which was trapped by the nucleophile **1.152**. Soon after, the scope of this reaction was extended to a variety of nitrogen nucleophiles,[190,191] as well as to the intramolecular version with aryl iodides bearing *ortho*-substituted nucleophilic groups and 1,4-dienes.[192] During these studies Larock also reported the selective 1,3-difunctionalisation of 1,4-cyclohexadienes.[189,190] Only recently, Yin further reported their the 1,3-arylboration and 1,3-diarylation of 1,4-cyclohexadienes.[193]



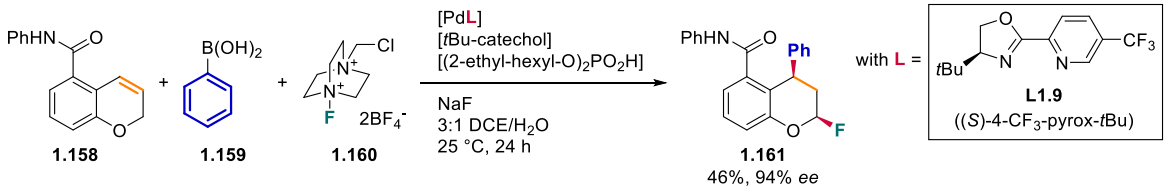
Scheme 1.24: Three-component migratory cross-coupling reaction of nonconjugated dienes.

During a study in 2004 on the synthesis of *N*-aryl pyrrolidines, Wolf observed the formation of a product issued from migration of the catalyst.[194] Further investigation led to a protocol furnishing 5-aryl octahydrocyclopenta[*b*]pyrroles (**1.157**) in good yields and excellent selectivity starting from alkenyl amine (**1.155**) and aryl bromide **1.156** when P(*t*Bu)$_2$Me (**L1.21**) was used as a ligand (Scheme **1.25**).[195] The effect of the ligand was quit dramatic in selectivity and reactivity, as switching to P(*t*Bu)$_3$ (**L1.3**) completely shut down the reaction.



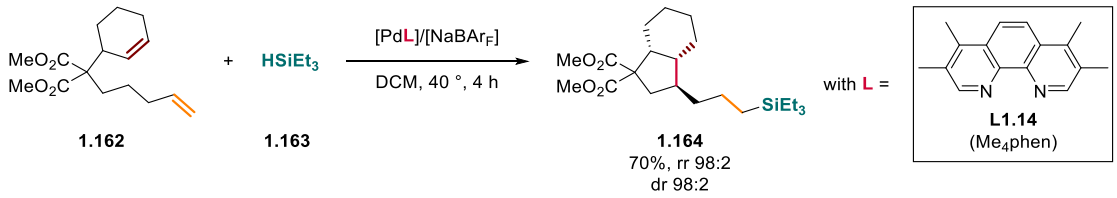
Scheme 1.25: Synthesis of 5-aryl octahydrocyclopenta[b]pyrroles involving chain-walking.

The possibility of an asymmetric 1,3-difunctionalisation on a cyclic system was reported by Toste in 2017 (Scheme **1.27**).[196] The integrated mechanistic study led the authors to conclude that the ligand, the aryl boronic acid (**1.159**) as well as the directing group significantly influence the regioselectivity of the reaction. Thus, an increased electrophilic character at palladium favoured the formation of the 1,3-product.



Scheme 1.26: 1,3-Arylfluorination of chromenes

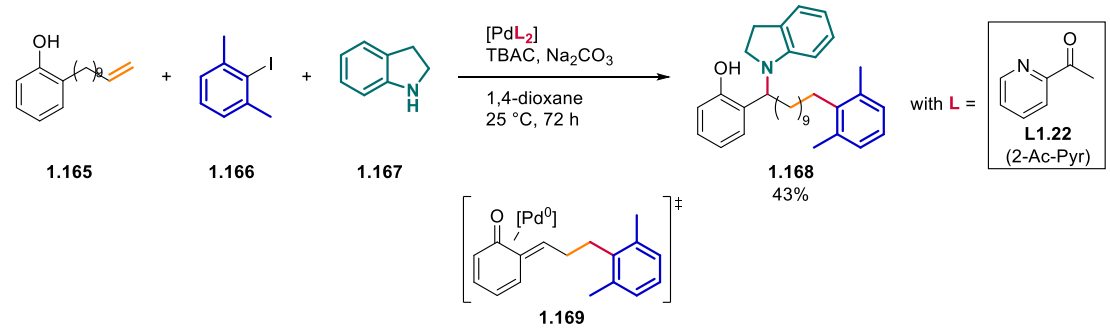
Kochi also recently disclosed the cycloisomerisation of remote dienes **1.162** initiated by hydrosilylation of the terminal alkene enabling further transformation at this end of the chain (Scheme **1.27**).[197]



1.162 **1.163** **1.164** 70%, rr 98:2 dr 98:2

Scheme 1.27: Hydrosilylation/cyclisation of remote dienes.

Finally Lin and Yao disclosed the 1,*x*-arylamination (*x* = 3-11) of unactivated alkenyl phenols (**1.165**, Scheme **1.28**).[198] They proposed a mechanism initiated by a Heck reaction followed by chain-walk to the remote benzylic position. Base-assisted quinone-methide formation (**1.169**) and subsequent aza-michael addition by indoline **1.167** furnishes the product **1.168**.



1.165 **1.166** **1.167** **1.168** 43% **1.169**

Scheme 1.28: 1,11-Arylamination of unactivated alkenyl phenols.

1.3.4. Conclusion

Site-specific remote functionalisation through migration of a palladium-catalyst along an alkyl-chain has gained significant momentum during the last decade. However, it has not always been an easy challenge to identify a terminating step, which selectively occurs at a specific site. Nevertheless, a broad range of reactions involving chain-walking have already been described. Furthermore, the field of remote functionalisation will surely grow continuously due to the large amount of reactions involving an alkyl-palladium species, which could be pushed to undergo migration.

Besides providing interesting scaffolds, it should also be noted that chain-walking further enables the regioconvergent functionalisation of positional mixtures of functionalised alkyl-chains such as fatty-acids or alkenes of interest for industrial valorisation of feed-stock chemicals.[25]

Moreover, in-depth mechanistic studies furnished valuable information on the different reaction parameters which influence the selectivity, and thus the researchers already have a strong background to rely on for further development.

1.4. Aim of this Thesis

The SMC is doubtless an indispensable tool for the synthesis of chemicals from fundamental academic research to large-scale industrial applications. Despite early observations of chain-walking during *B*-alkyl SMC and a constantly growing number of migratory cross-coupling reactions, the development of an efficient palladium-catalysed migratory version of the SMC has remained elusive.

The aim of this thesis was therefore to design and develop a migratory version of the SMC to further broaden the organic chemist's toolbox as well as to gain additional insights in the reaction parameters influencing chain-walking.

In the first part, we will discuss the efforts made towards a one-pot approach for the regioconvergent terminal arylation of regioisomeric mixtures of alkenes. Since lightweight alkenes represents a cheap feedstock, this would represent an efficient way to bring some molecular complexity in a single step.

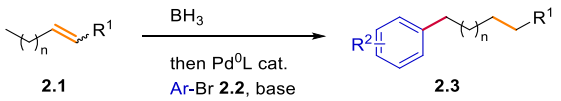
The second part will be dedicated to the development of the benzylic selective migratory SMC for the synthesis of 1,1-diarylalkenes starting from alkenes, borane and bromoarenes.

Finally, attempts towards the development of a cascade reaction involving the benzylic selective migratory SMC followed by a C(sp^2)-H activation to furnish fluorenes will be presented.

2. Terminal-Selective Palladium-Catalysed Migratory Suzuki-Miyaura Cross-Coupling

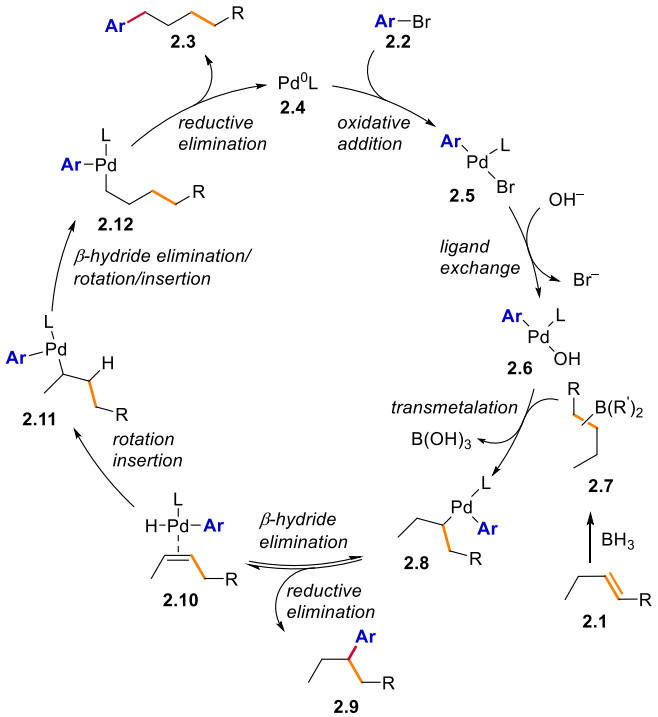
2.1. Design Plan

Linear alkenes are an important feedstock obtained amongst others through cracking of crude oil. However, the resulting crude is composed of isomeric mixtures, which leads to tedious purification and thus rising the price of the final product.[199] Hence, a method which could selectively functionalise a regioisomeric mixture of linear alkenes in a regioconvergent manner is highly desirable. As described in Section **1.3**, alkenes can readily undergo migratory cross-coupling. With this in mind, we envisioned that we could exploit terminal-selective palladium-catalysed migratory SMC for the remote functionalisation of alkenes as shown in Scheme **2.1**.



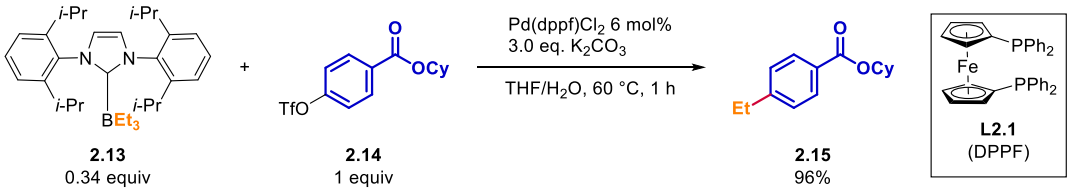
Scheme 2.1: Aim of the project: terminal-selective remote functionalisation through migratory SMC.

A hypothetic catalytic cycle for this transformation is depicted in Scheme **2.2**. Oxidative addition of the electrophile **2.2** to a Pd^0 catalyst (**2.4**) followed by ligand exchange gives the intermediate **2.6**. Transmetalation with the alkylborane **2.7** obtained by alkene hydroboration yields the intermediate **2.8** which then undergoes chain-walking until it reaches a terminal position yielding the intermediate **2.12**. Reductive elimination at this site furnishes the linear alkylarene product **2.3** and regenerates the catalyst **2.4**.



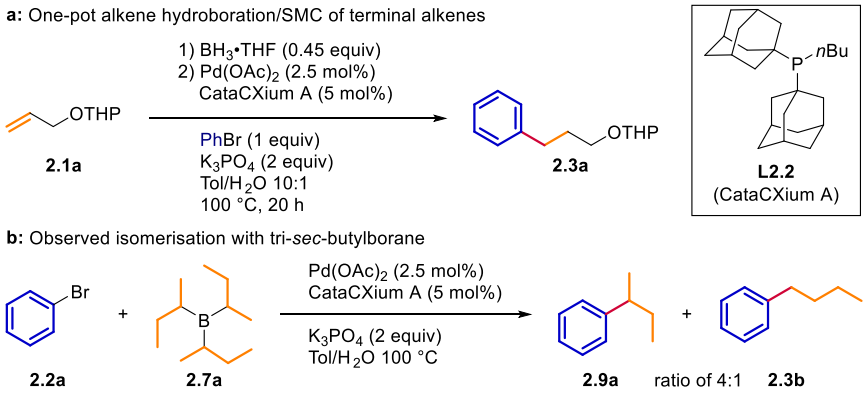
Scheme 2.2: Hypothetic catalytic cycle.

Ideally, all three alkyl moieties of the trialkylborane species **2.7** would undergo transmetalation successively. However, previous SMC protocols employing linear trialkylborane generally engage an excess amount of the borane species due to side-reactions and slow transmetalation rates.[200,201] In order to enhance the reactivity of trialkylboranes, Lacôte envisioned to exploit their complexation with an *N*-heterocyclic carbene (NHC).[202] Thus, all three alkyl-substituents of this complex could be successfully transformed to the alkylarene product **2.15** when a base was added to the reaction mixture. However, the stoichiometric amount of NHC used translates to a poor overall atom-economy (Scheme **2.3**).



Scheme 2.3: SMC of NHC-Boranes enables the transfer of all three alkyl moieties of symmetrical trialkylboranes.

More recently, Li and Zhong reported a one-pot procedure for the generation and SMC of linear trialkylboranes with aryl halides (Scheme **2.4a**).[203] Interestingly, they observed isomerisation when the reaction was performed with tri-*sec*-butylborane **2.7a**, yielding a 4:1 mixture of the direct **2.9a** and migratory cross-coupling products **2.3b** (Scheme **2.4b**). Thus, this report served as inspiration for the design as well as proof-of-concept for the idea of a terminal-selective migratory SMC.



Scheme 2.4: One-pot procedure for the SMC of terminal alkenes and observed isomerisation for the SMC with tri-*sec*-butylborane.

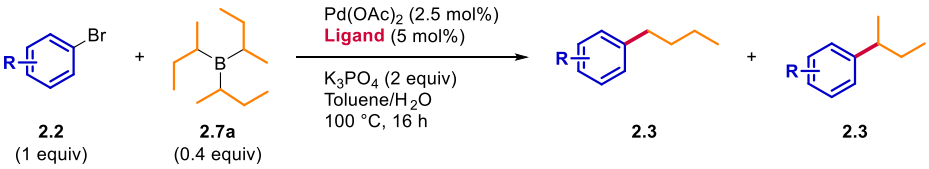
2.2. Results & Discussion

2.2.1. Preliminary Test-Reactions

We initiated our studies by reproducing the protocol of Li and Zhong[203] with CataCXium A (**L2.2**) or RuPhos (**L2.3**) as ligand, tri-*sec*-butylborane (**2.7a**) and different bromoarenes (**2.2**) to identify the reaction parameters which influence the chain-walking process (Table **2.1**). As described, the coupling of bromobenzene (**2.2a**) and tri-*sec*-butylborane (**2.7a**) with CataCXium A (**L2.2**) as ligand furnished a mixture of branched

and linear product with a linear/branched ratio of ~1:4 (entry **1**). A dramatic difference in selectivity was observed when the reaction was performed with RuPhos (**L2.3**) as ligand, indicating a strong influence of the ligand on the selectivity (entry **2**). Interestingly, the electronic parameters of the electrophile **2.2** only had a slight impact (entry **3**-**5**), whereas a higher ratio of the linear product **2.3** was observed when 1-bromo-2-fluorobenzene (**2.2d**) was used as electrophile as previously observed (entry **6, 7**).[157,166] CataCXium PnBu (**L2.4**), which provided optimal selectivity in previous migratory Negishi cross-couplings,[162–166] gave better ratios albeit with low yields and mainly dehalogenated electrophile as side-product (entry **8**, **9**).

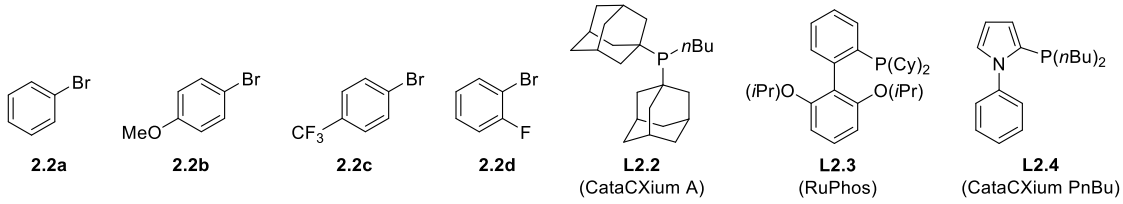
Table 2.1: Preliminary test-reactions.



2.2 (1 equiv) + **2.7a** (0.4 equiv) → **2.3** + **2.3**

Entry	Ligand	ArBr	rr[a]
1	CataCXium A (**L2.2**)	**2.2a**	18:82
2	RuPhos (**L2.3**)	**2.2a**	5:95
3	CataCXium A (**L2.2**)	**2.2b**	21:79
4	RuPhos (**L2.3**)	**2.2b**	18:82
5	CataCXium A (**L2.2**)	**2.2c**	32:67
6	CataCXium A (**L2.2**)	**2.2d**	95:5
7	RuPhos (**L2.3**)	**2.2d**	50:50
8	CataCXium PnBu (**L2.4**)	**2.2b**	81:19
9	CataCXium PnBu (**L2.4**)	**2.2c**	66:34

[a] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



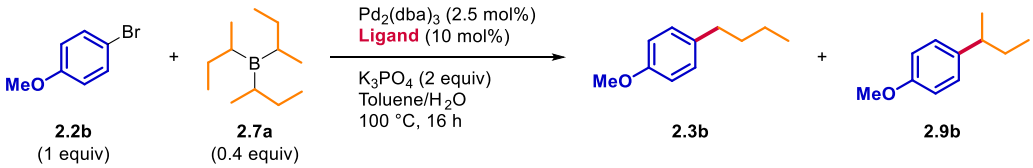
2.2a **2.2b** **2.2c** **2.2d** **L2.2** (CataCXium A) **L2.3** (RuPhos) **L2.4** (CataCXium PnBu)

The high differences in selectivity between the conditions tested indicate a strong influence from the ligand, but only minimal influence from the electronic parameters of the electrophile. Thus, we reasoned it is possible to identify the right catalyst in order to achieve the set goal of a regioisomeric ratio of minimum 9:1 for the linear product **2.3**. An additional challenge expected to be encountered is the finding of the right conditions to enable the efficient transmetalation of all three *sec*-alkyl moieties of the trialkylborane species **2.7**. However, an alternative to overcome this problem is the preparation of the *sec*-alkylboronic acid analogue by adjusting the equivalents of borane used for the hydroboration of the alkene **2.1**, as this specie were previously successfully engaged in SMC (*see also* Section **1.2.3**)

2.2.2. Optimisation of the Reaction Conditions

We initiated our study with the model reaction of 4-bromoanisole (**2.2b**) and tri-*sec*-butylborane (**2.7a**) to focus on the migratory SMC, thus avoiding the initial hydroboration step. Aiming at identifying a potent family of ligands for our reaction, we performed a broad screen of ligands (Table **2.2** and **2.3**). Interestingly, a 82:18 regioisomeric ratio was observed when JohnPhos (**L2.5**) was used (entry **1**, Table **2.2**), but this selectivity was lost when the alkyl substituents of the ligand were different (entry **2**, **3**). DavePhos (**L2.8**) and PhDavePhos (**L2.9**) roughly gave a 1:1 mixture of products (entry **4**, **5**). Further phenyl-pyrrole-type or related ligands were also tested, but yielded only poor regioisomeric ratios (entry **6**-**11**).

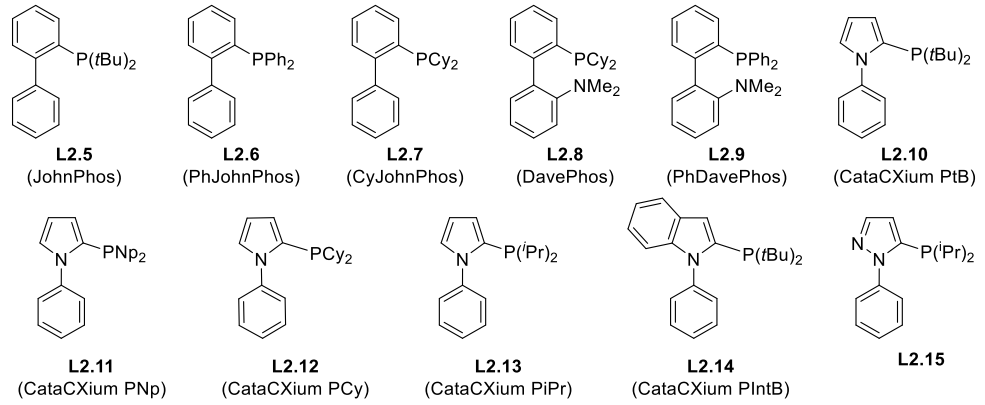
Table 2.2: Initial screening of ligands (1/2).



2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	JohnPhos (**L2.5**)	16	82:18
2	PhJohnPhos (**L2.6**)	11	57:43
3	CyJohnPhos (**L2.7**)	30	39:61
4	DavePhos (**L2.8**)	39	44:56
5	PhDavePhos (**L2.9**)	19	49:51
6	CataCXium PtB (**L2.10**)	6	64:36
7	CataCXium PNp (**L2.11**)	20	43:57
8	CataCXium PCy (**L2.12**)	21	22:78
9	CataCXium PiPr (**L2.13**)	23	36:64
10	CataCXium PIntB (**L2.14**)	18	63:37
11	**L2.15**	29	13:87

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

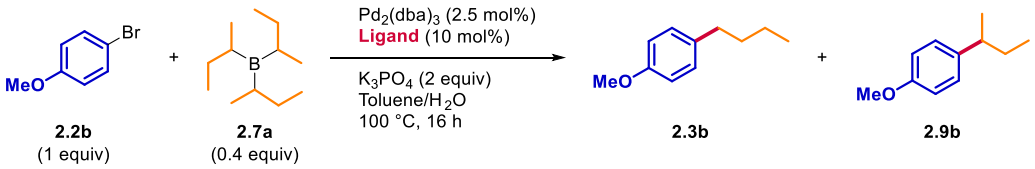


L2.5 (JohnPhos), **L2.6** (PhJohnPhos), **L2.7** (CyJohnPhos), **L2.8** (DavePhos), **L2.9** (PhDavePhos), **L2.10** (CataCXium PtB), **L2.11** (CataCXium PNp), **L2.12** (CataCXium PCy), **L2.13** (CataCXium PiPr), **L2.14** (CataCXium PIntB), **L2.15**

We then continued the ligands screen with smaller phosphines (Table **2.3**). Phenyl substituents on the phosphine further gave poor selectivity (entry **1**, **2**), while PCy_3 (**L2.18**)

gave an interesting 80:20 ratio, but with only 5% yield (entry **3**), which could be increased to 53% with similar selectivity when the corresponding tetrafluoroborate salt **L2.19** was engaged (entry **4**). The more bulky P(*t*Bu)$_3$·HBF$_4$ (**L2.20**) gave mainly the direct coupling product, eventually giving us a clue on which parameters of the ligand could influence the selectivity (entry **5**). However, further trialkyl-phosphines did not clarify if smaller ligands indeed favour the chain-walking (entry **6**-**12**). Bidentate ligands further yielded unsatisfying mixtures of the coupling products.

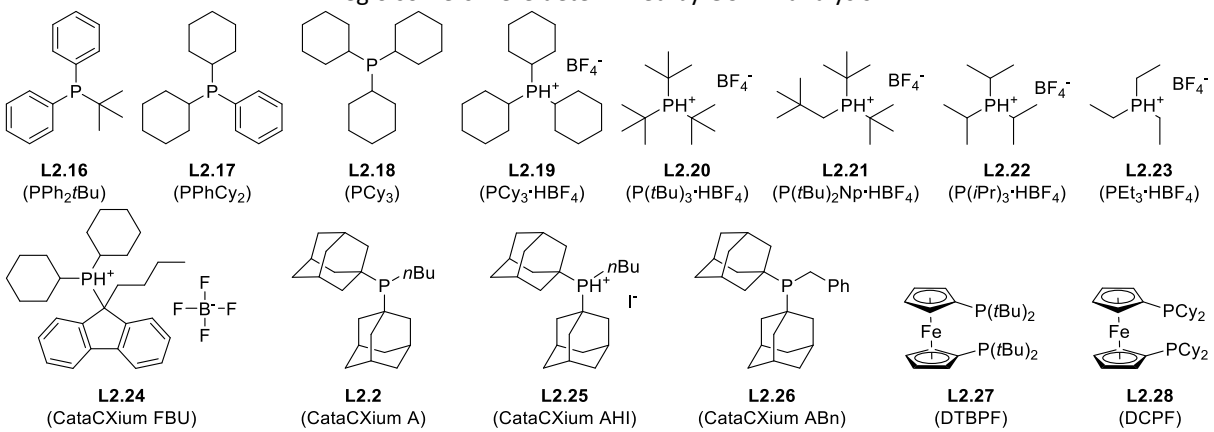
Table 2.3: Initial screening of ligands (2/2).



2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	PPh$_2$*t*Bu (**L2.16**)	55	31:69
2	PPhCy$_2$ (**L2.17**)	54	53:47
3	PCy$_3$ (**L2.18**)	5	80:20
4	PCy$_3$·HBF$_4$ (**L2.19**)	53	77:23
5	P(*t*Bu)$_3$·HBF$_4$ (**L2.20**)	72	24:76
6	P(*t*Bu)$_2$Np·HBF$_4$ (**L2.21**)	61	73:27
7	P(*i*Pr)$_3$·HBF$_4$ (**L2.22**)	9	83:17
8	PEt$_3$·HBF$_4$ (**L2.23**)	-	-
9	CataCXium FBU (**L2.24**)	11	52:48
10	CataCXium A (**L2.2**)	76	19:81
11	CataCXium AHI (**L2.25**)	10	21:79
12	CataCXium ABn (**L2.26**)	2	46:54
13	DTBPF (**2.27**)	29	19:81
14	DCPF (**L2.28**)	37	53:47

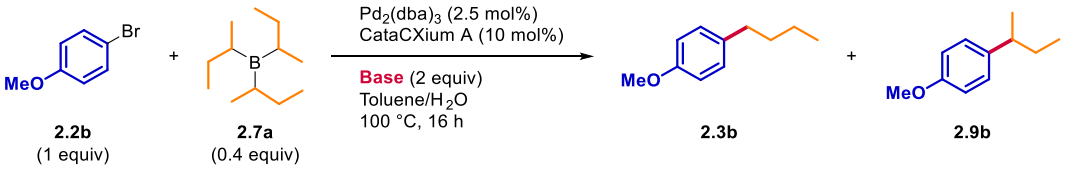
[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



As the reaction mostly gave poor overall yields, we decided to enhance the reactivity before screening further ligands. Thus, as the base can play a major role in SMC, we tested various

inorganic bases which are traditionally used in SMC with the initial reaction conditions (Table **2.4**). The reaction seemed to work, but without improvement, with hydroxide bases (entry **1**-**3**), as well as *tert*-butoxide bases (entry **4**-**6**). Lithium carbonate completely shut down the reaction (entry **7**) but potassium carbonate gave 72% combined yield (entry **8**). Caesium carbonate gave a slightly better yield (entry **9**) than the initial conditions with potassium phosphate (*see also* Table **2.3**, entry **10**), whereas acetates completely killed the reactivity (**11**-**13**). We retained caesium carbonate as it gave a slight increase in yield, but also because it facilitated the filtration over Celite® during the work-up of the reactions. Surprisingly, changing the amount of caesium carbonate did not give great differences (entry **1**-**3**, Table **2.5**).

Table 2.4: Screening of different inorganic bases.

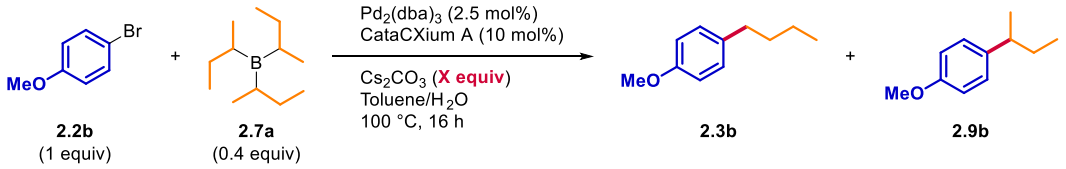


2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Base	Combined Yield (%)[a]	rr[b]
1	LiOH	39	19:81
2	NaOH	64	19:81
3	KOH	71	19:81
4	LiO*t*Bu	50	19:81
5	NaO*t*Bu	70	19:81
6	KO*t*Bu	74	19:81
7	Li_2CO_3	-	-
8	K_2CO_3	72	19:81
9	Cs_2CO_3	79	19:81
10	LiOAc	-	-
11	NaOAc	-	-
12	KOAc	-	-

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

Table 2.5: Screening of the amount of base.



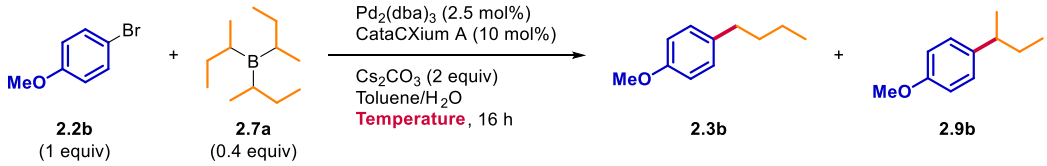
2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Amount of Base	Combined Yield (%)[a]	rr[b]
1	1.0 equiv.	71	18:82
2	1.5 equiv.	75	18:82
3	3.0 equiv.	80	18:82

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

We then turned our attention to the reaction temperature (Table **2.6**). Interestingly, lowering the temperature gave a faintly better selectivity for the linear product (entry **1**), whereas higher temperature slightly decreased the selectivity (entry **3**). However, we decided to keep the temperature at 100 °C as we observed decreased reactivity with other phosphines at 80 °C.

Table 2.6: Screening of different temperatures.



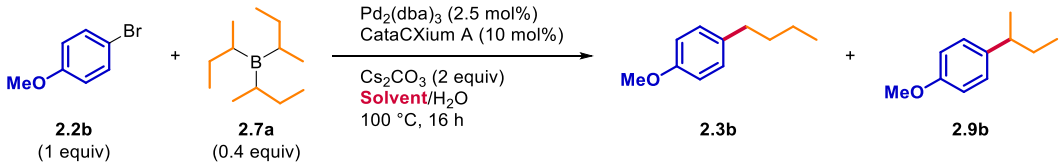
2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Temperature (°C)	Combined Yield (%)[a]	rr[b]
1	80	78	21:79
2	100	79	18:82
3	120	76	16:84

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

Finally we also tested different solvents (Table **2.7**). Ether solvents generally gave a slightly better selectivity compared to toluene, but decreased the reactivity (entry **1-5**). Acetonitrile and 1,2-dichloroethane also lowered the reactivity (entry **7,8**), and hexane did not give any improvement either (entry **9**). Thus, it seemed that a 10:1 mixture of toluene with water was the best solvent system.

Table 2.7: Screening of solvents.



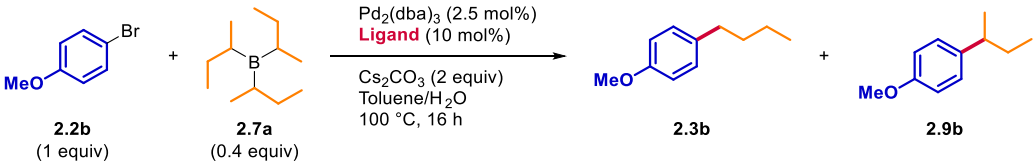
2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Solvent	Combined Yield (%)[a]	rr[b]
1	THF	44	23:77
2	2-MeTHF	45	22:78
3	DME	43	24:76
4	*t*-BME	45	23:77
5	1,4-Dioxane	52	23:77
6	MeCN	38	22:78
7	DCE	34	28:72
8	Hexane	69	20:80

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

With slightly improved conditions at hand, we turned our focus back to the main goal of improving the regioselectivity of the reaction. Various *N*-heterocyclic carbene (NHC) were tested, but unfortunately showed no reactivity for this type of reaction (Table **2.8**, entry **1**-**7**).

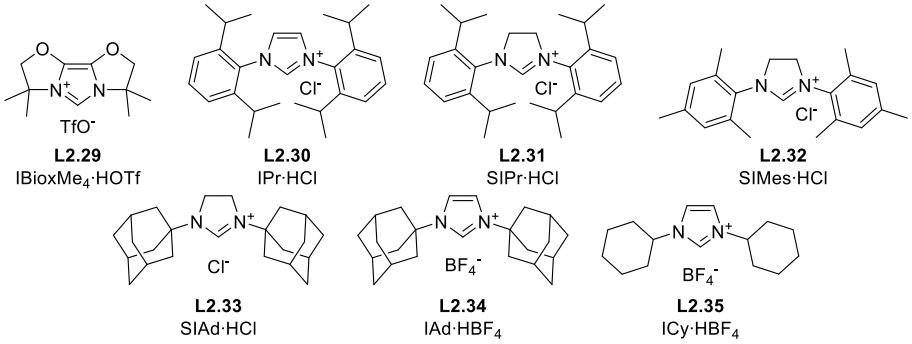
Table 2.8: Screening of NHC ligands.



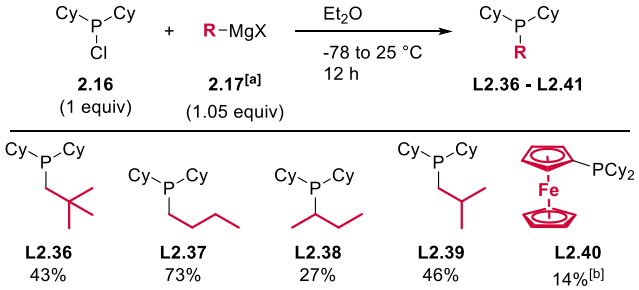
2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	IBioxMe$_4$·HOTf (**L2.29**)	-	-
2	IPr·HCl (**L2.30**)	~1	60:40
3	SIPr·HCl (**L2.31**)	-	-
4	SIMes·HCl (**L2.32**)	-	-
5	SIAd·HCl (**L2.33**)	-	-
6	IAd·HBF$_4$ (**L2.34**)	-	-
7	ICy·HBF$_4$ (**L2.35**)	-	-

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



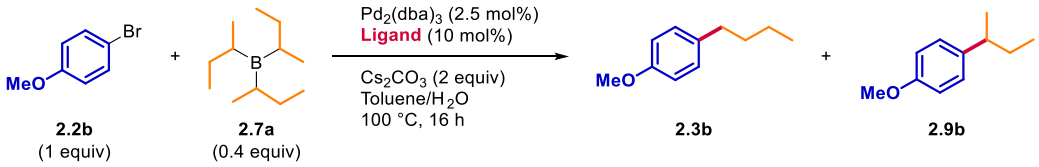
Since PCy$_3$·HBF$_4$ (**L2.19**) gave the best results in the previous ligand screenings with similar reaction conditions (*see also* Table **2.3**, entry **4**), we decided to change one cyclohexyl substituent and thus tune the steric properties, which seemed to affect the regioselectivity. Therefore, six new PCy$_2$R (**L2.36 – L2.40**) were successfully synthesized from chlorodicyclohexylphosphine (**2.16**) and the corresponding Grignard reagents (**2.17**, Scheme **2.5**).



Scheme 2.5: Synthesis of PCy$_2$R; [a] X = Br, Cl; [b] Prepared from the corresponding lithiate.

These newly synthesised ligands were then tested in the model reaction with additional commercial ligands (Table **2.9**). Surprisingly, a slightly smaller[204] neopentyl substituent (**L2.36**) completely switched the selectivity to the direct coupling product (entry **1**), whereas in a previous ligand screening the P(*t*Bu)$_2$Np·HBF$_4$ (**L2.21**) gave a much better selectivity for the linear product than P(*t*Bu)$_3$·HBF$_4$ (**L2.20**, *see also* Table **2.3**, entry **5**, **6**). Linear alkyl substituents gave a better selectivity at the expense of reactivity (entry **2**) which was more pronounced for *n*-butyl (entry **3**). Only small yields and worsened selectivity was observed with branched butyl isomers (entry **4**, **5**). The ferrocene containing phosphine **L2.41** gave a ~1:1 mixture and a similar outcome was obtained when PCy$_2$*t*Bu (**L2.42**) was tested (entry **8**). The bidentate DCPE (**L2.43**) showed no reactivity (entry **9**). As we assumed that less steric bulk favours the chain-walk we also tested PCyp$_3$ (**L2.44**), which indeed gave a better selectivity than the cyclohexyl analogue (entry **10**).

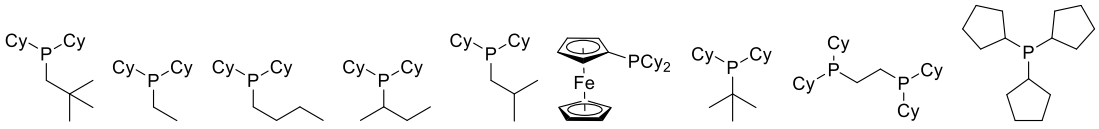
Table 2.9: Screening of PCy$_2$Alk ligands.



2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

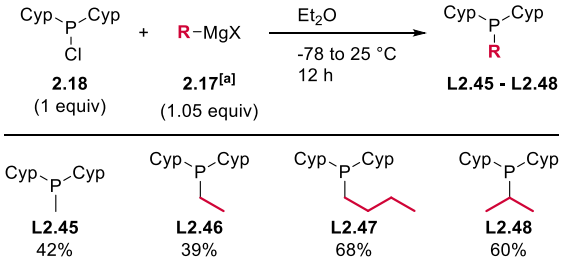
Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	PCy$_2$Np (**L2.36**)	48	26:74
2	PCy$_2$Et (**L2.41**)	44	87:13
3	PCy$_2$*n*Bu (**L2.37**)	4	88:12
4	PCy$_2$*s*Bu (**L2.38**)	17	78:22
5	PCy$_2$*i*Bu (**L2.39**)	10	70:30
6	PCy$_2$Fer (**L2.40**)	53	51:49
8	PCy$_2$*t*Bu (**L2.42**)	70	46:54
9	DCPE (**L2.43**)	-	-
10	PCyp$_3$ (**L2.44**)	51	83:17

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



L2.36 (PCy$_2$Np) **L2.41** (PCy$_2$Et) **L2.37** (PCy$_2$*n*Bu) **L2.38** (PCy$_2$*s*Bu) **L2.39** (PCy$_2$*i*Bu) **L2.40** (PCy$_2$Fer) **L2.42** (PCy$_2$*t*Bu) **L2.43** (DCPE) **L2.44** (PCyp$_3$)

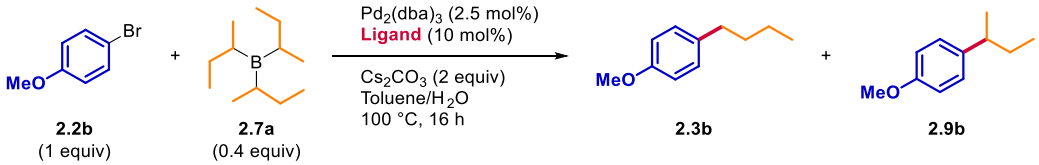
Motivated by this promissing result, we assumed that the smaller PCyp$_2$Alk analogues could further improve the selectivity and thus we prepared a small library of such phosphines (Scheme **2.6**).



Scheme 2.6: Synthesis of PCyp$_2$Alk; [a] X = Br, Cl.

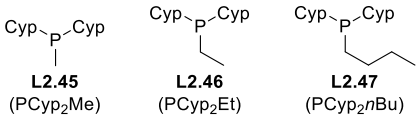
The reaction with PCyp$_2$Me (**L2.45**) did not give any product (entry **1**), and the two PCyp$_2$Alk phosphines with either an ethyl **L2.46** or a *n*-butyl **L2.47** gave comparable results regarding selectivity and low yields (entry **2**, **3**).

Table 2.10: Screening of PCyp$_2$Alk ligands.

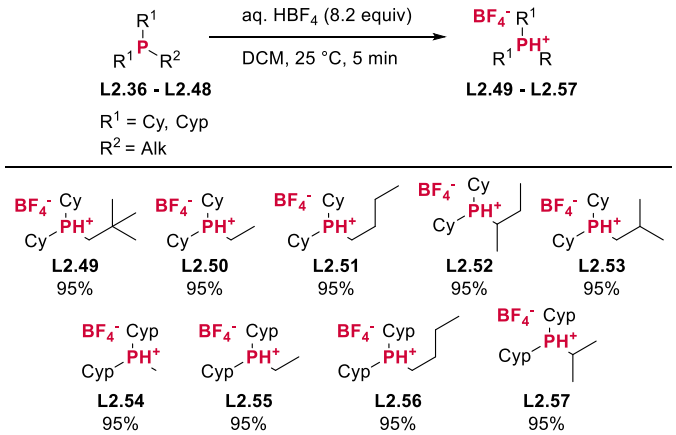


Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	PCyp$_2$Me (**L2.45**)	-	-
2	PCyp$_2$Et (**L2.46**)	38	88:12
3	PCyp$_2$*n*Bu (**L2.47**)	5	89:11

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



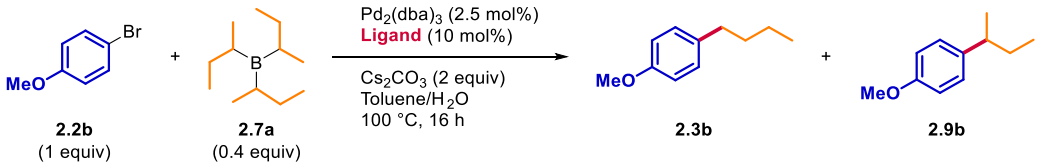
Since, the reactivity with these ligands seemed very delicate, and the tetrafluoroborate salt of PCy$_3$ **L2.19** previously showed better results in terms of yield (*see also* Table **2.3**, entry **3**, **4**), we decided to prepare the salts of the previously obtained phosphines by simply mixing them with aqueous HBF$_4$ in dichloromethane (Scheme **2.7**).[205]



Scheme 2.7: Synthesis of the HBF$_4$ salts from the corresponding trialkylphosphines.

The obtained ligands **L2.49** – **L2.53** and **L2.54** – **L2.57** as well as the commercial **L2.58** were then engaged in the model reaction to check if the reactivity could be enhanced (Table **2.11**). Unfortunately, all of the $PCy_2Alk{\cdot}HBF_4$ ligands **L2.49 – L2.53** and **L2.58** did not significantly improve the yield of the reaction (entry **1**-**6**), whereas the reactions with $PCyp_2Alk{\cdot}HBF_4$ **L2.54** – **L2.57** showed minor improvements (entry **7**-**10**). Interestingly, despite with a very low yield, we observed for the first time a selectivity of above 9:1 for the linear product with $PCyp_2Me{\cdot}HBF_4$ **L2.55** (entry **7**), as well as with $P(nBu)_3$ **L2.59** (entry **11**).

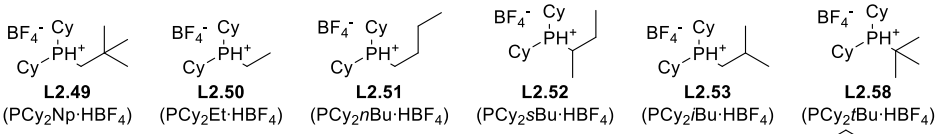
Table 2.11: Screening of PCy_2Alk and $PCyp_2Alk$ tetrafluoroborates.

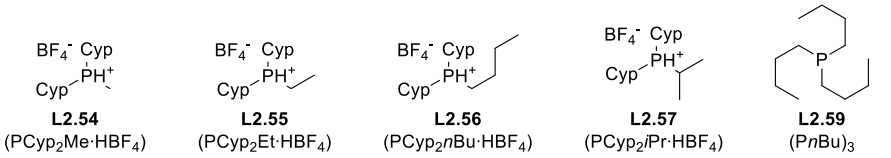


2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	$PCy_2Np{\cdot}HBF_4$ (**L2.49**)	60	28:72
2	$PCy_2Et{\cdot}HBF_4$ (**L2.50**)	41	87:13
3	$PCy_2nBu{\cdot}HBF_4$ (**L2.51**)	6	87:13
4	$PCy_2sBu{\cdot}HBF_4$ (**L2.52**)	26	78:22
5	$PCy_2iBu{\cdot}HBF_4$ (**L2.53**)	19	69
6	$PCy_2tBu{\cdot}HBF_4$ (**L2.58**)	56	46:54
7	$PCyp_2Me{\cdot}HBF_4$ (**L2.54**)	~1	93:7
8	$PCyp_2Et{\cdot}HBF_4$ (**L2.55**)	44	88:12
9	$PCyp_2nBu{\cdot}HBF_4$ (**L2.56**)	36	87:13
10	$PCyp_2iPr{\cdot}HBF_4$ (**L2.57**)	54	81:19
11	$PnBu_3$ (**L2.59**)	~1	95:5

[a] Yield determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

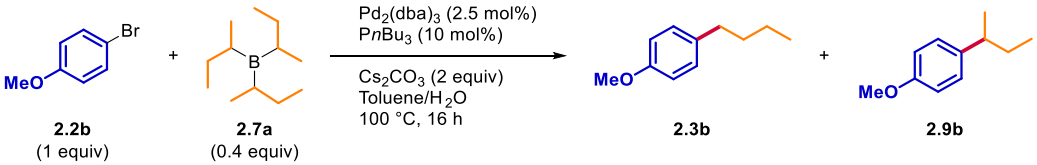




Since we finally had a good regioselectivity, we turned our attention to the reactivity. As we observed only trace amounts of product, we started with the investigation of the key steps of the migratory SMC. Thus, we tested various additives which we believed could enhance the transmetalation e.g. by coordination to the borane (Table **2.12**). However, while nitrogen or phosphorous Lewis bases did not improve the yield (entry **1**, **2**), interestingly, silver salts showed some minor improvements which could be associated to the removal of the bromide in the reaction mixture by forming insoluble silver-halide salts and thus making the palladium more cationic (entry **3**, **4**). A further hint in this direction was the complete absence of product

when lithium triflate was used (entry **5**). Lithium chloride, which has been observed to enhance the reactivity in other cross-couplings,[6] did not increase the yield (entry **6**).

Table 2.12: Screening of different additives.



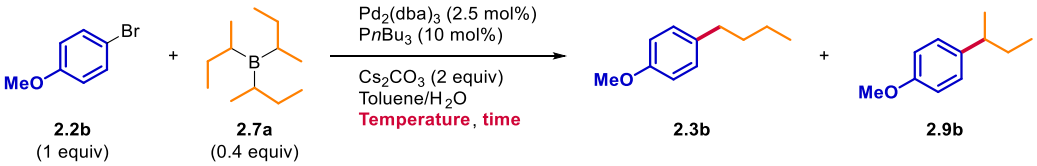
2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Additive	Combined Yield (%)[a]	rr[b]
1	DABCO (0.4 equiv)	-	-
2	P*n*Bu$_3$ (0.4 equiv)	~1	95:5
3	AgOTf (1 equiv)	11	92:8
4	AgBF$_4$ (1 equiv)	3	93:7
5	LiOTf (1 equiv)	-	-
6	LiCl (1 equiv)	-	-

[a] Yield of **2.3b** determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

We therefore continued our optimisation study by testing the reaction at different temperatures and a prolonged reaction time (Table **2.13**). Decreasing the temperature was detrimental (entry **1**, **2**), and prolonged reaction time not beneficial (entry **1**-**3**). A higher temperature was also not improving the yield (entry **4**).

Table 2.13: Longer reaction time and different temperatures.



2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

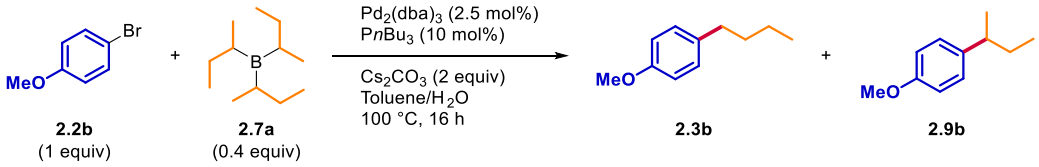
Entry	Temp. (°C)	Reaction time	Combined Yield (%)[a]	rr[b]
1	60	4.5 d	11	94:6
2	80	4.5 d	31	93:7
3	100	4.5 d	49	92:8
4	120	16 h	27	91:9

[a] Yield of **2.3b** determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

Another possible way of generating more cationic palladium intermediates is to use different types of the electrophile. We therefore tested various pseudo-halides (Table **2.14**). Aryl-tosylate **2.19** and the aryl-mesylate **2.20** showed no reactivity (entry **1**, **2**). However, the aryl-triflate **2.21a** gave 49% yield with a high regioisomeric ratio of 92:8 (entry **3**) and also the aryl-nonaflate **2.22a** gave a similar outcome (entry **4**). The aryl-diazonium salt **2.23**, which tends to give a very cationic palladium intermediate upon oxidative addition as well as the

generally more reactive aryl-iodide did not react (entry **5**, **6**). Thus, we continued with the aryl-triflate **2.21a**.

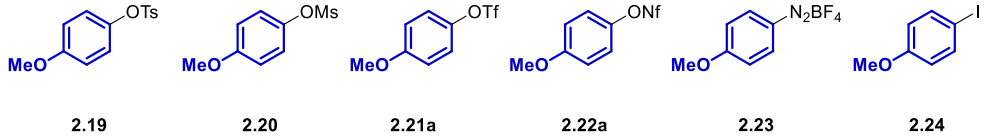
Table 2.14: Screening of different types of electrophiles.



2.2b (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Electrophile	Combined Yield (%)[a]	rr[b]
1	Aryl-Tosylate (**2.19**)	-	-
2	Aryl-Mesylate (**2.20**)	-	-
3	Ar-Triflate (**2.21a**)	49	92:8
4	Ar-Nonaflate (**2.22a**)	42	92:8
5	Aryl-Diazonium·HBF_4 (**2.23**)	-	-
6	Ar-Iodide (**2.24**)	-	-

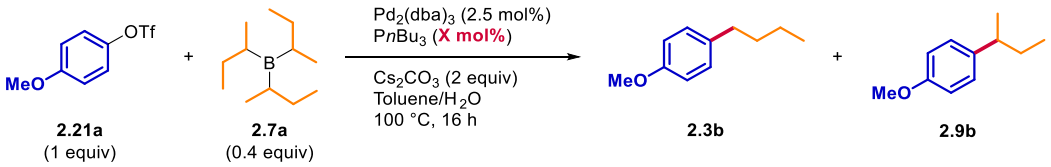
[a] Yield of **2.3b** determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



2.19 **2.20** **2.21a** **2.22a** **2.23** **2.24**

We also investigated the palladium-to-ligand ratio, which can have an impact on various stages of the reaction as previously described (*see also* Section **1.2.2.**). A 1:1 ratio seemed to give a slightly lower yield (entry **1**) compared to the previously used 1:2 ratio (entry **2**), whereas a 1:3 ratio nearly shut down the reactivity (entry **3**). Therefore we concluded to maintain the original amount of ligand.

Table 2.15: Screening of the palladium – ligand ratio.



2.21a (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

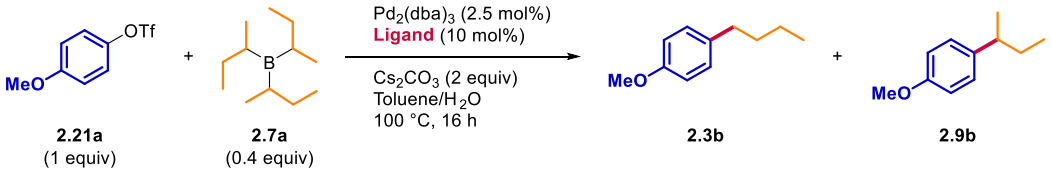
Entry	Amount of Ligand	Combined Yield (%)[a]	rr[b]
1	5 mol%	40	92:8
2	10 mol%	50	92:8
3	15 mol%	6	95:5

[a] Yield of **2.3b** determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

As the employment of aryl-triflate **2.21a** significantly enhanced the yield, we decided to test some ligands which previously either did not give any product, or showed interesting selectivity but with low yield (Table **2.16**). Symmetrical trialkylphosphines gave modest yield with good selectivity (entry **1-3**), and the ethyl substituted dicycloalkylphosphines showed

some conversion with high selectivity (entry **4**, **5**). The reaction with $PCyp_2Me$, which previously gave a yield of 1% (*see also* Table **2.11**, entry **7**) now furnished 47% of the product in a 91:9 ratio (entry **6**). Other substituents did not improve the results (entry **7**, **8**), but 82% yield with a ratio of 88:12 was obtained when $P(tBu)_2Me$ **L2.60** was engaged (entry **9**). Finally, the reaction with NHC ligands also yielded some product, but with a poor selectivity (entry **10,11**).

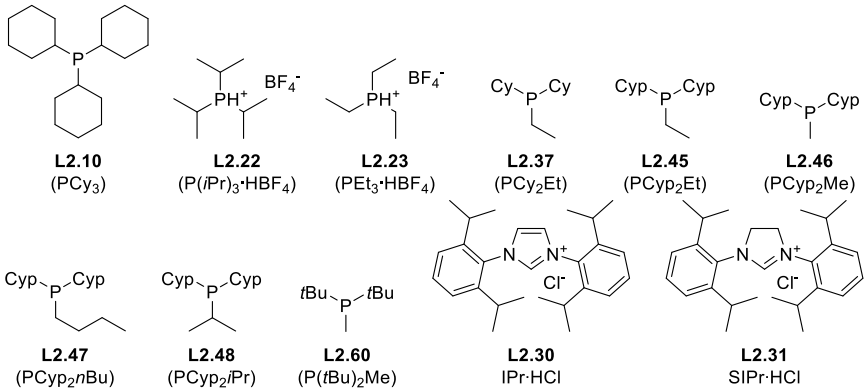
Table 2.16: Screening of ligands with aryl triflate **2.21b**.



2.21a (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

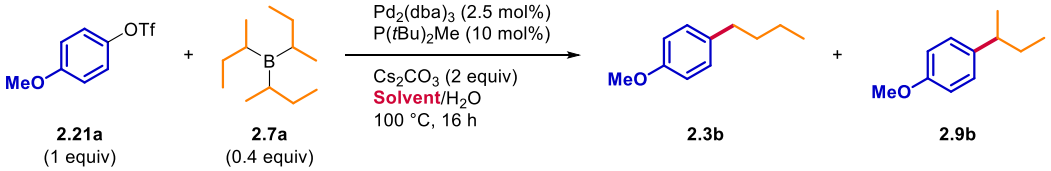
Entry	Ligand source	Combined Yield (%)[a]	rr[b]
1	PCy_3 (**L2.10**)	34	78:22
2	$PiPr_3{\cdot}HBF_4$ (**L2.22**)	38	82:18
3	$PEt_3{\cdot}HBF_4$ (**L2.23**)	36	93:7
4	PCy_2Et (**L2.37**)	49	87:13
5	$PCyp_2Et$ (**L2.45**)	33	89:11
6	$PCyp_2Me$ (**L2.46**)	47	91:9
7	$PCyp_2nBu$ (**L2.47**)	15	88:12
8	$PCyp_2iPr$ (**L2.48**)	36	82:18
9	$P(tBu)_2Me$ (**L2.60**)	82	88:12
10	IPr·HCl (**L2.30**)	11	53:47
11	SIPr·HCl (**L2.31**)	2	44:56

[a] Yield of **2.3b** determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.



An additional screening of different solvents was then performed in a final attempt of reaching the set goal of a 9:1 ratio in favour of the linear product with $P(tBu)_2Me$ **L2.60** (Table **2.17**). Amide solvents slightly improved the selectivity at the expense of the yield (entry **1-3**). Other polar aprotic solvents also decreased the yield of the reaction (entry **4**, **5**), whereas alcohol solvents shut down the reactivity (entry **6**, **7**). Ether solvents as well as acetonitrile and DCE also showed no improvement (entry **8-10**).

Table 2.17: Screening of solvents.

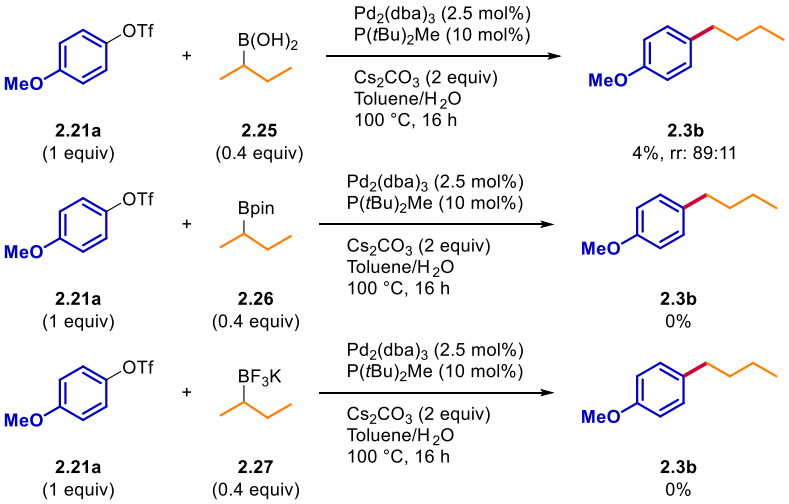


2.21a (1 equiv) + **2.7a** (0.4 equiv) → **2.3b** + **2.9b**

Entry	Solvent	Combined Yield (%)[a]	rr[b]
1	DMF	18	90:10
2	NMP	23	90:10
3	DMAC	29	90:10
4	Et_3N	62	87:13
5	EtOAc	43	89:11
6	*i*PrOH	1	93:7
7	EtOH	2	91:7
8	THF	25	89:11
9	1,4-Dioxane	48	89:11
10	DME	61	90:10
11	MeCN	13	91:9
12	DCE	9	90:10

[a] Yield of **2.3b** determined by GC-FID analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

We then performed some test-reactions with different *sec*-butylborane species to see if the reaction conditions are generally applicable (Scheme **2.8**). The reaction surprisingly only gave 4% of product with *sec*-butylboronic acid **2.25**, which is thought to be the species generated *in situ* after two transmetalation starting from the tri-*sec*-butylborane **2.7a**. Furthermore, the pinacol ester **2.26** and the trifluoroborate analogues **2.27** did not furnish any product at all.



2.21a (1 equiv) + **2.25** (0.4 equiv) → **2.3b** 4%, rr: 89:11

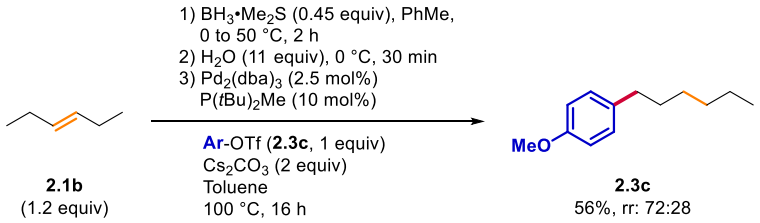
2.21a (1 equiv) + **2.26** (0.4 equiv) → **2.3b** 0%

2.21a (1 equiv) + **2.27** (0.4 equiv) → **2.3b** 0%

Scheme 2.8: Test-reactions with different *sec*-butylboranes. Yield determined by GC-FID analysis with internal standard; Regioisomeric ratio (rr) of linear/branched regioisomers were determined by GC-FID analysis.

As outlined at the beginning of this chapter (*see also* Scheme **2.1**), the aim of this project was to start from an olefin which undergoes hydroboration followed by migratory SMC. Initial

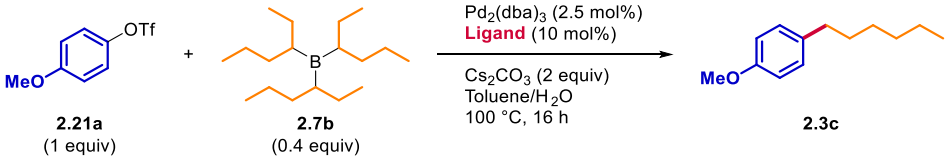
attempts for the hydroboration of *trans*-3-hexene **2.1b** using the same protocol as reported by Li and Zhong[203] surprisingly yielded no product. However, after minor modifications we were pleased to find that adding the alkene to a 2 M BH_3·DMS solution in toluene at room temperature and letting the reaction mixture stir for 1 hour at 50 °C efficiently transformed the olefin to the tri-3-hexyl-borane **2.7b**. With the hydroboration working we then tested the whole sequence (Scheme **2.9**). The reaction starting with *trans*-3-hexene **2.1b** furnished 56% yield of **2.3c**, but with a modest 72:28 regioisomeric ratio for the linear product over the sum of the branched isomers. The drop in selectivity, and to some extend the lower yield, can be rationalised by the longer migration distance necessary to reach the terminal position of the alkyl-chain. This also means, that the yield and selectivity would possibly further drop if the reaction is performed with longer linear alkene chains.



Scheme 2.9: One-pot alkene hydroboration/migratory SMC test-reaction. The initial position of the alkene is highlighted in orange. Yield determined by GC-MS analysis with internal standard; Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.

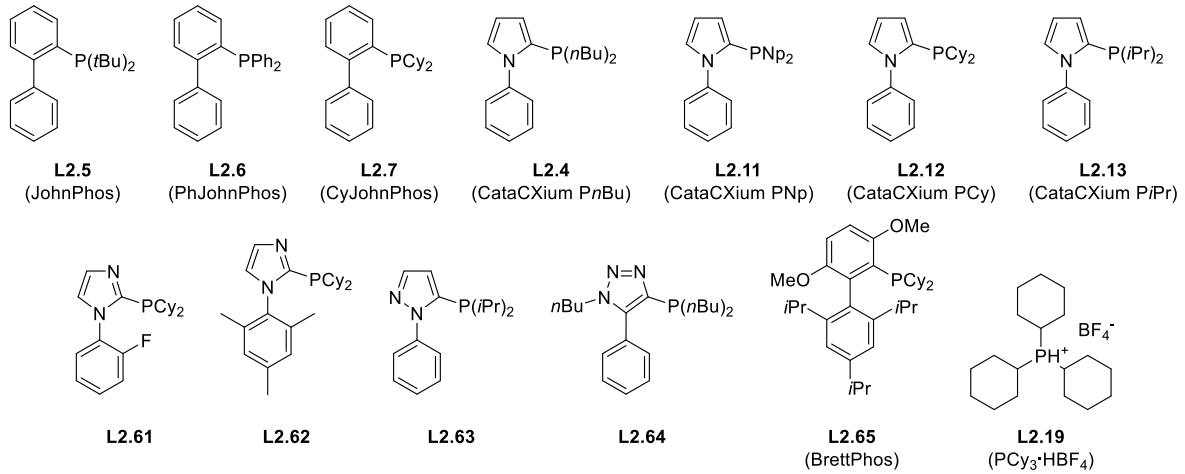
We therefore had to perform further optimisation, but this time starting from tri-3-hexyl-borane **2.7b** in order to adapt our reaction conditions to longer branched chains. Thus, different classes of ligands were again tested, to see whether we could identify another ligand platform suitable for the migratory SMC (Table **2.18**). Unfortunately, the biphenyl-type ligands performed only poorly (entry **1**, **3**), even though JohnPhos **L2.5** gave a better selectivity of 83:17 (entry **1**). Phenyl-pyrrole or related ligands also showed only little reactivity and selectivity (entry **4**-**7**). Other *N*-aromatic phosphines as well as BrettPhos **L2.4** were also not performing well (entry **8**-**12**).

Table 2.18: Screening of ligands with **2.26**.



Entry	Ligand source	Yield (%)[a]	rr[b]
1	JohnPhos (**L2.5**)	16	83:17
2	PhJohnPhos (**L2.6**)	10	45:55
3	CyJohnPhos (**L2.7**)	10	41:59
4	CataCXium P*n*Bu (**L2.4**)	17	64:36
5	CataCXium PNp (**L2.11**)	-	-
6	CataCXium PCy (**L2.12**)	6	21:79
7	CataCXium P*i*Pr (**L2.13**)	7	48:52
8	**L2.61**	2	57:43
9	**L2.62**	6	14:86
10	**L2.63**	3	51:49
11	**L2.64**	28	75:25
12	BrettPhos (**L2.65**)	4	27:73
13	$PCyp_3 \cdot HBF_4$ (**L2.19**)	21	78:22

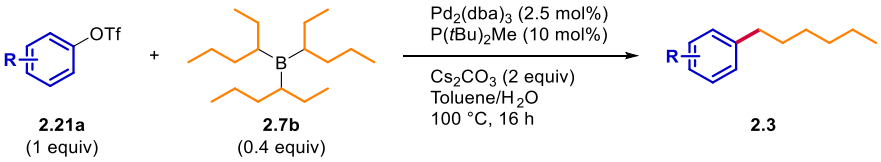
[a] Yield of **2.3c** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.



Since we could not identify a better catalyst system to achieve a higher regioselectivity, we then turned our attention towards the electrophile. As the chain-walking process occurs after oxidative addition and transmetalation, the electrophile is ligated to the palladium during the migration of the catalyst along the alkyl-chain, and thus can influence the steric and electronic properties of the catalyst (*see also* Scheme **2.2**). Electron withdrawing substituents in *ortho*-position to the electrophilic centre generally disfavours the reductive elimination electronically, and therefore favour the chain-walk as observed for the initial test-reactions (*see also* Table **2.1**, entry **6**, **7**) as well as in previous reports from the Baudoin group.[157,166] We engaged different electrophiles to gain further insight and identify a potential substituent, which could serve as a directing group (Table **2.19**). An electron withdrawing substituent such

as a trifluoromethyl in *para*-position (**2.21b**) gave a 88:12 ratio for the linear product (entry **1**), whereas an electron donating substituent such as a methoxy at the same position (**2.21a**) gave an 72:28 ratio (entry **2**) and a methyl (**2.21c**) led to a 80:20 ratio (entry **3**). A trifluoromethyl group in *meta*-position (**2.21d**) further slightly improved the selectivity (entry **4**). To our delight, a methoxy substituent in *ortho*-position (**2.21e**) gave rise to an excellent selectivity of >99:1 (entry **5**), as with a trifluoromethyl substituent (**2.21f**) (entry **6**). An *ortho*-methyl (**2.21g**) on the other hand furnished a 95:5 ratio (entry **7**). These results indicated that the steric influence of a substituent in *ortho*-position is sufficient under the optimised reaction conditions to achieve the linear cross-coupling product through migratory SMC with an excellent selectivity. In pursuit of identifying an easily removable directing group, we further tested the reaction with an *ortho*-chloride substituted electrophile (**2.21h**), obtaining the linear product with an excellent regioisomeric ratio but only 15% yield (entry **8**).

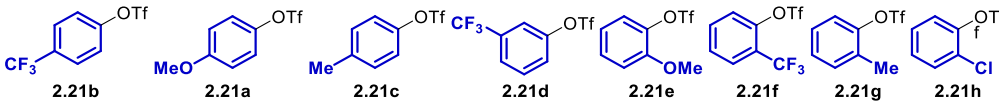
Table 2.19: Investigating the influence of the electrophile on the regioselectivity.



2.21a (1 equiv) + **2.7b** (0.4 equiv) → **2.3**

Entry	Electrophile	Yield (%)[a]	rr[b]
1	*para*-CF_3 **2.21b**	*n.d.*	88:12
2	*para*-OMe **2.21a**	56	72:28
3	*para*-Me **2.21c**	*n.d.*	80:20
4	*meta*-CF_3 **2.21d**	*n.d.*	91:9
5	*ortho*-OMe **2.21e**	*n.d.*	>99:1
6	*ortho*-CF_3 **2.21f**	*n.d.*	>99:1
7	*ortho*-Me **2.21g**	58	95:5
8	*ortho*-Cl **2.21h**	15	>99:1

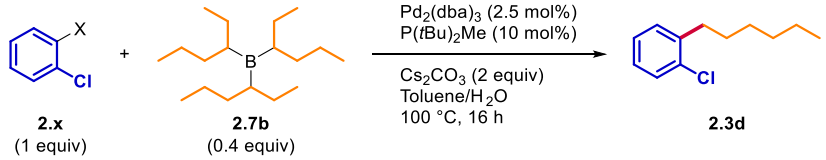
[a] Yield of **2.3** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.



2.21b **2.21a** **2.21c** **2.21d** **2.21e** **2.21f** **2.21g** **2.21h**

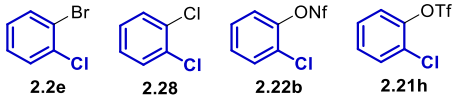
As the electronic parameters can also influence the other stages of the reaction we tested different 2-chloro substituted electrophiles (Table **2.20**). The linear product **2.3d** was obtained in 32% yield with 1-bromo-2-chlorobenzene **2.2e** (entry **1**), and in 19% with 1,2-dichlorobenzene **2.28** (entry **2**) as electrophiles with a >99:1 ratio. As expected, the 2-chlorophenyl nonaflate **2.22b** (entry **3**) did not improve when compared to the reaction with 2-chlorophenyl triflate **2.21h** (entry **4**). A possible reason for the low yield for the reaction with 2-chlorophenyl triflate **2.21h** could be the formation of benzyne.

Table 2.20: Screening of different types of electrophiles.



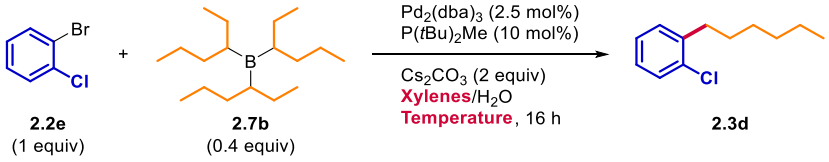
Entry	Electrophile	Yield (%)[a]	rr[b]
1	Ar-Bromide **2.2e**	32	>99:1
2	Ar-Chloride **2.28**	19	>99:1
3	Ar-Nonaflate **2.22b**	7	>99:1
4	Ar-Triflate **2.21h**	15	>99:1

[a] Yield of **2.3d** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.



We then moved on to see whether we could increase the reactivity with higher temperature (Table **2.21**). To avoid overpressure in the reaction system we decided to uses xylenes as solvent instead of toluene. The reaction gave a similar yield at 100 °C (entry **1**), demonstrating the viability of the new solvent. Increasing the temperature to 120 °C significantly increased the yield to 69% (entry **2**). Further increase in temperature only gave slightly higher yield (entry **3**, **4**) so we decided to retain 120 °C as the best compromise between the harshness of the reaction conditions and yield.

Table 2.21: Screening of higher temperatures with xylenes instead of toluene.

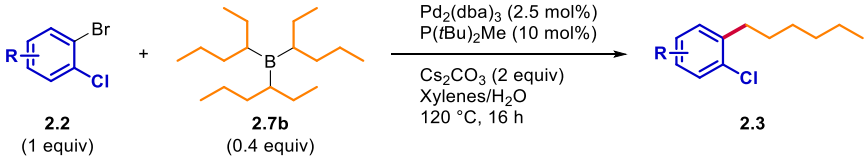


Entry	Temperature (°C)	Yield (%)[a]	rr[b]
1	100	32	>99:1
2	120	69	>99:1
3	130	72	>99:1
4	140	75	>99:1

[a] Yield of **2.3d** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.

With these conditions in hand we moved on to see how the reaction proceeds with additional substituents on the electrophile (Table **2.22**). Intriguingly the reaction performed poorly with methoxy substituted 1-bromo-2-chlorobenzenes (entry **1-3**) as well as with methyl benzoates (entry **4-7**).

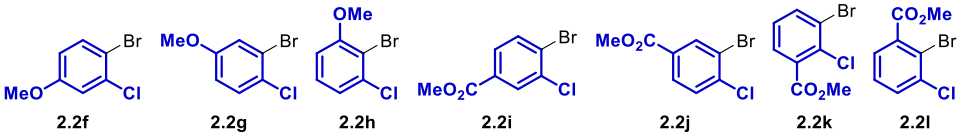
Table 2.22: Reactivity check with substituted 1-bromo-2-chlorobenzenes.



2.2 (1 equiv) **2.7b** (0.4 equiv) **2.3**

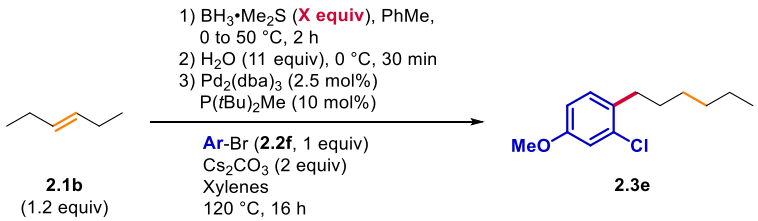
Entry	Electrophile	Yield (%)[a]	rr[b]
1	Aryl-bromide **2.2f**	20	>99:1
2	Aryl-bromide **2.2g**	53	>99:1
3	Aryl-bromide **2.2h**	2	>99:1
4	Aryl-bromide **2.2i**	-	-
5	Aryl-bromide **2.2j**	32	>99:1
6	Aryl-bromide **2.2k**	34	>99:1
7	Aryl-bromide **2.2l**	-	-

[a] Yield of **2.3** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.



Changing the amount of borane used for the hydroboration and therefore generating different *sec*-alkyl borane species of *trans*-3-hexene **2.1b** only slightly improved the yield with the 4-methoxy substituted electrophile **2.2f**, indicating that the species of the organoborane is not an issue of the reaction (Table **2.23**).

Table 2.23: Screening of the amount of borane used.



2.1b (1.2 equiv) **2.3e**

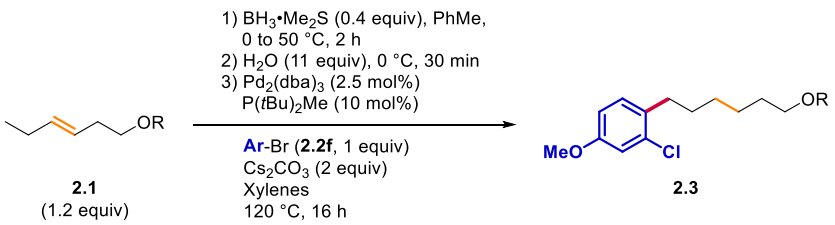
Entry	Amount of BH_3·DMS	Yield (%)[a]	rr[b]
1	0.4	28	>99:1
2	0.8	26	>99:1
3	1.2	30	>99:1

[a] Yield of **2.3e** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.

As the reactions were conducted at a quite high temperature, we hypothesized that maybe the transient alkenes generated during the chain-walking process could dissociate from the catalyst and evaporate in the gaseous phase. Thus we prepared various protected alkenyl alcohols to see if heavier substrates would lead to increased yields (Table **2.24**). The reaction with the pivalate **2.1c** did not produce any product (entry **1**), but the THP **2.1d** and benzyl protected **2.1e** substrates gave slightly improved yields (entry **2**, **3**) compared to

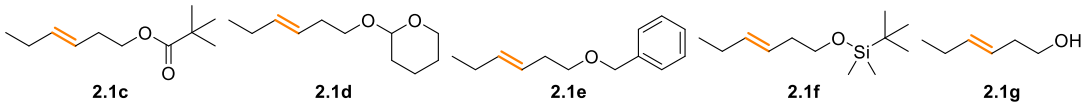
trans-3-hexene **2.1b**. Additionally, the silyl protected **2.1f** and the free alkenyl alcohol **2.1g** gave no product (entry **4**, **5**).

Table 2.24: Testing less volatile substrates.

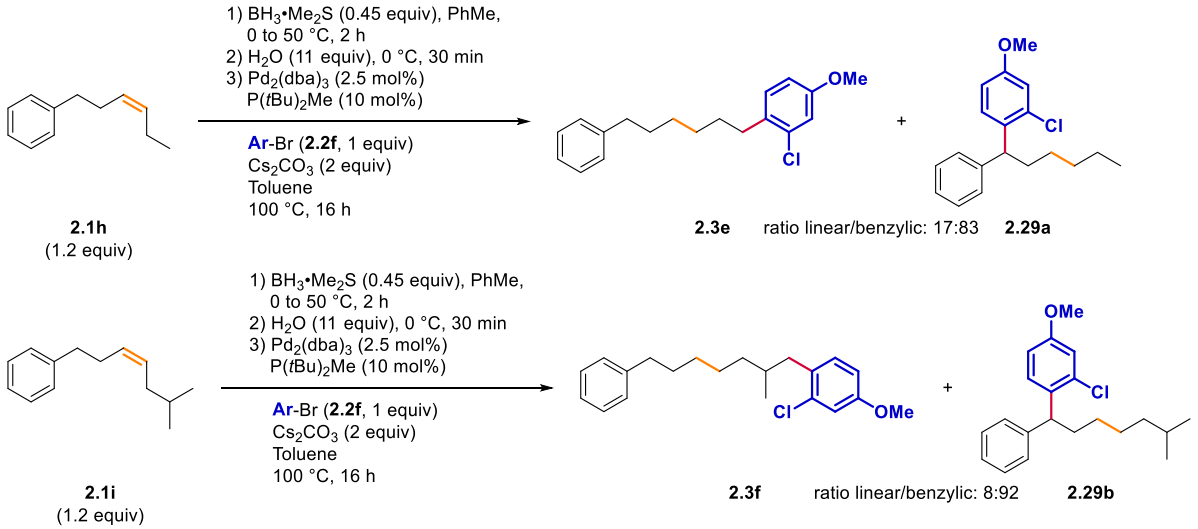


Entry	Olefin	Yield (%)[a]	rr[b]
1	2.1c	-	-
2	2.1d	55	>99:1
3	2.1e	53	>99:1
4	2.1f	-	-
5	2.1g	-	-

[a] Yield of **2.3** determined by GC-MS analysis with internal standard; [b] Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis.

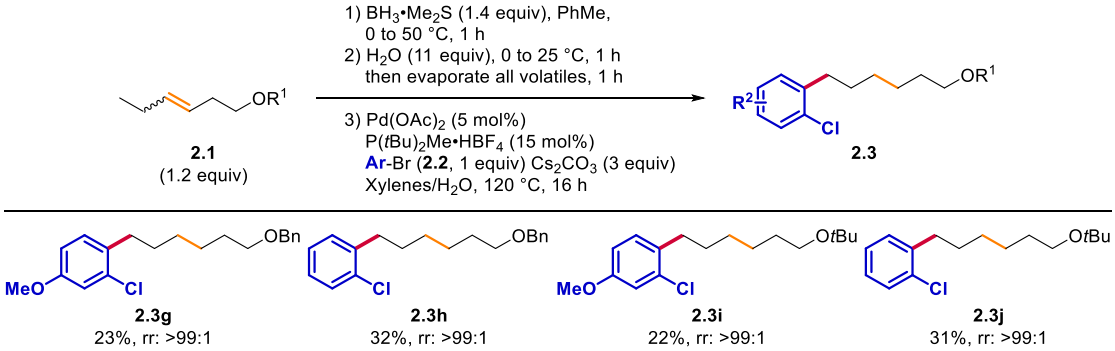


We then investigated alkenyl arenes as substrates. Interestingly, we observed a competition between the formation of the linear product **2.3e** and the 1,1-diarylalkane product **2.29a** when the reaction was performed with the alkenyl arene **2.1h** (Scheme **2.10**). It seemed that the reductive elimination was considerably enhanced at the benzylic position and thus favouring the remote functionalisation at the benzylic site. It is also noteworthy to mention that the catalyst was able to undergo migration over a *tertiary* position as observed when the reaction was performed with alkenyl arene **2.1i**.



Scheme 2.10: One-pot alkene hydroboration/migratory SMC test-reactions. Yield not determined; Regioisomeric ratio (rr) of linear/benzylic regioisomers were determined by GC-MS analysis.

Additional optimisation efforts finally led to some minor changes to the reaction conditions. Thus, more stable and reproducible results were obtained by employing $Pd(OAc)_2$ as palladium source, which is reduced *in situ* by one equivalent of the phosphine ligand in a 3:1 ratio with the palladium and three equivalents of the base. However, only modest yields were obtained for the terminal-selective migratory SMC of protected alkenyl alcohols (Scheme **2.11**).



Scheme 2.11: Examples of the linear selective SMC. The initial position of the alkene is highlighted in orange. Yields refer to the isolated product. Regioisomeric ratio (rr) of linear/sum of branched regioisomers were determined by GC-MS analysis of the crude reaction mixture.

With these results we decided to discontinue this project and went on to design a different approach for the development of a migratory SMC.

2.3. Conclusion

In summary, the goal of converting a regioisomeric mixture of alkenes to alkyl arenes in a regioconvergent manner through a sequence of hydroboration and migratory SMC only gave unsatisfactory yields, despite the excellent achieved regioselectivity.

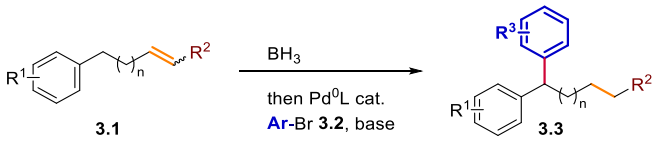
Considerable efforts were made through intensive screening of various parameters of the reaction conditions and valuable insights were gained for future projects. Despite the ability of palladium catalysts to undergo efficient reductive elimination at a terminal position as disclosed by a multitude of direct as well as some migratory cross-coupling protocols, it appears that the changes made during the optimisation to favour the migration of the catalyst was detrimental to the overall reactivity.

Late results with alkenyl arenes showed an interesting competition for the reductive elimination, furnishing mainly the product issued from the reductive elimination at the benzylic site. Therefore, we decided to discontinue this project and proceed with the development of a benzylic-selective migratory SMC, which will be discussed in the following chapter.

3. Benzylic-Selective Palladium-Catalysed Migratory Suzuki-Miyaura Cross-Coupling

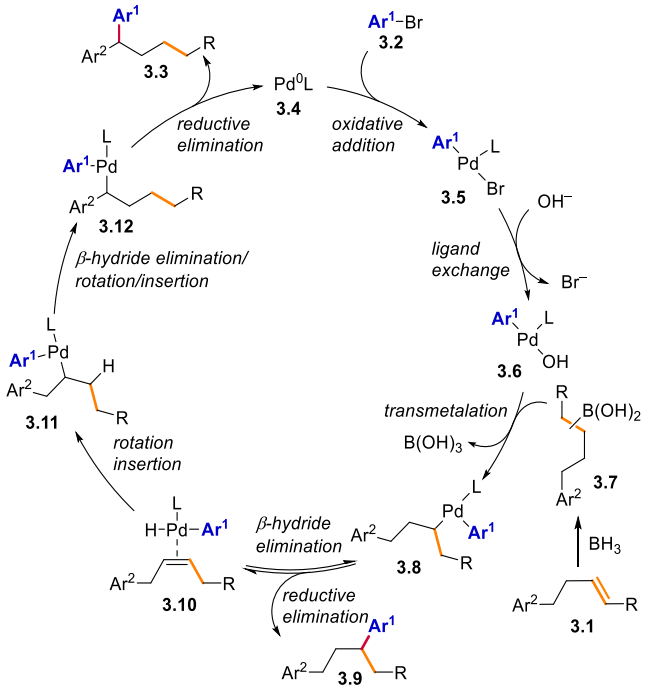
3.1. Design Plan

As described at the end of Chapter **2** (Scheme **2.10**), when we investigated alkenyl arenes in our reaction, we observed a competition for the reductive elimination between the terminal and the benzylic site, yielding mainly the product arylated in benzylic position. With this in mind we envisioned that we could exploit benzylic-selective migratory SMC for the remote functionalisation of alkenyl arenes at the benzylic site yielding 1,1-diarylalkanes as shown in Scheme **3.1**.



Scheme 3.1: Aim of the project: benzylic-selective remote functionalisation through migratory SMC.

A hypothetic catalytic cycle, analogous to the terminal-selective palladium catalysed migratory SMC is depicted in Scheme **3.2**. Oxidative addition of the electrophile **3.2** to a Pd^0 catalyst (**3.4**) followed by ligand exchange gives the intermediate **3.6**. Transmetalation with the alkylboranonic acid **3.7** obtained by alkene hydroboration yields the intermediate **3.8** which then undergoes chain-walking until it reaches a benzylic position yielding the intermediate **3.12**. Reductive elimination at this site furnishes the 1,1-diarylalkane **3.3** and regenerates the catalyst **3.4**.



Scheme 3.2: Hypothetic catalytic cycle.

The unsymmetrically substituted 1,1-diarylalkane structural motif is present in natural as well as synthetic bioactive molecules (Figure **3.1**),[206–210] but only a few examples of direct palladium catalysed cross-coupling of benzylic organoboranes exist.[83,211–215] Besides recent reports on nickel-catalysed benzylic-selective migratory arylations[216–218] and a selective migratory allylic arylation reaction,[219] to the best of our knowledge this work represents the first example of a palladium-catalysed benzylic-selective SMC of B-alkyl boronic acids and aryl halides.

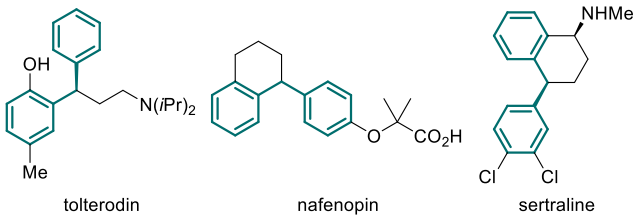
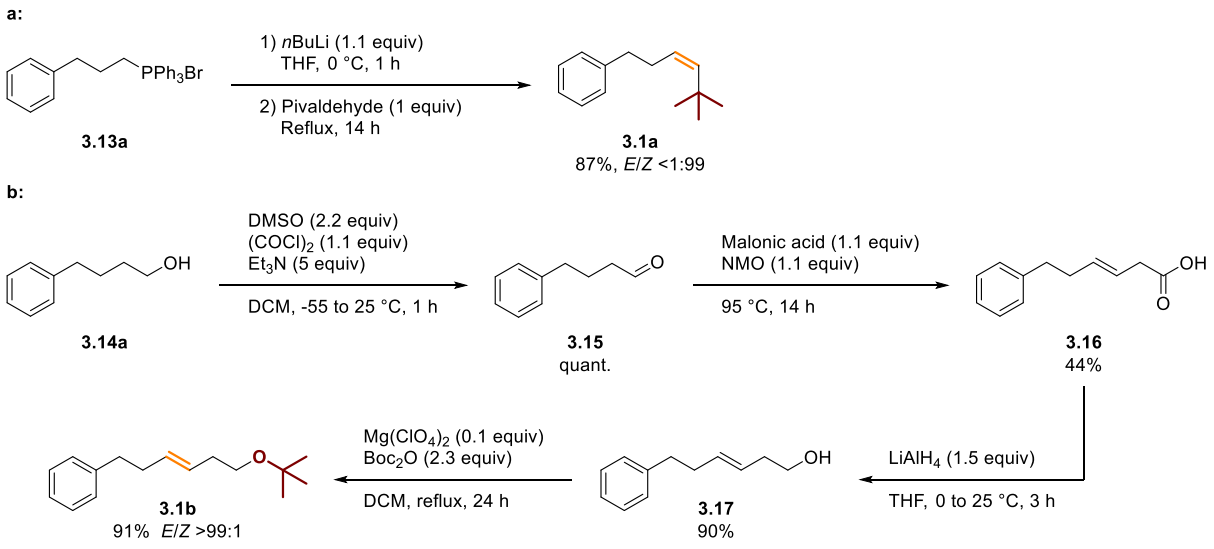


Figure 3.1: Bioactive 1,1-diarylalkanes.

3.2. Results and Discussion

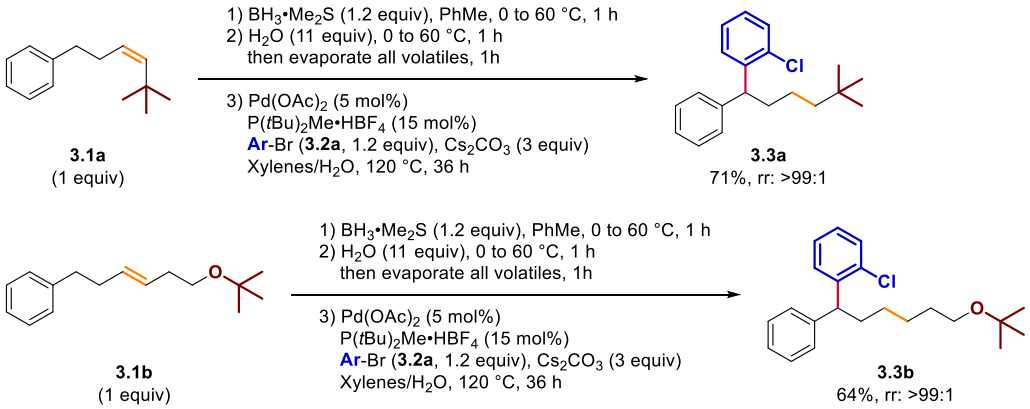
3.2.1. Preliminary Test-Reactions

We initiated our studies with the preparation of alkenyl arenes **3.1** bearing a group which would block the chain-walking of the catalyst, and thus favour the selective formation of 1,1-diarylalkanes **3.3**, with a minimal distance of two methylene bonds for the chain-walking. The alkene **3.1a** bearing a *tert*-butyl blocking group was obtained through a Wittig reaction of triphenylphosphonium bromide **3.13a** and pivaldehyde (Scheme **3.3a**). Additionally, a more extended alkene **3.1b** with a protected alcohol moiety as a blocking group was prepared through reduction and protection of the carboxylic acid **3.16**, obtained through a modified Knoevenagel condensation of the aldehyde **3.15** generated by a Swern oxidation of 4-phenylbutanol (**3.14a**, Scheme **3.3b**).



Scheme 3.3: Synthesis of **3.1a** and **3.1b**.

The obtained substrates **3.1a** and **3.1b** were then engaged in the one-pot alkene hydroboration/migratory SMC with 1-bromo-2-chlorobenzene (**3.2a**). Delightfully, we observed exclusive benzylic regioselectivity for both substrates when using P(*t*Bu)$_2$Me·HBF$_4$ (**L3.1**) as ligand, furnishing the products **3.3a** and **3.3b** in decent yields (Scheme **3.4**). Notably, either geometry of the initial alkene, *Z* for **3.1a** and *E* for **3.1b**, yielded the corresponding intermediate alkylboronic acid species **3.7** efficiently.



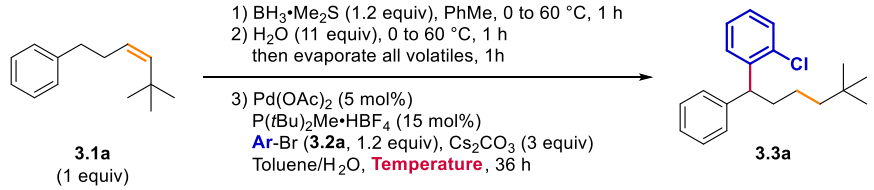
Scheme 3.4: Test-reactions with different blocking groups for the terminal position.

3.2.2. Optimisation of the Reaction Conditions

We then moved on with the optimisation of the reaction conditions with (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**3.1a**) together with *ortho*-substituted aryl electrophile **3.2a** and P(*t*Bu)$_2$Me·HBF$_4$ (**L3.1**) as ligand. We retained the borane dimethylsulfide complex as cheap and easy-to-handle hydroboration agent since the regioselectivity of the initial hydroboration step does not affect the outcome of the reaction.

We started by performing the reaction at different temperatures (Table **3.1**). The reactivity decreased significantly with lower temperatures (entry **1**, **2**), and slightly lower yields were obtained when toluene (entry **3**) was replaced by xylenes (entry **4**), but without affecting the regioselectivity.

Table 3.1: Screening of the reaction temperature.

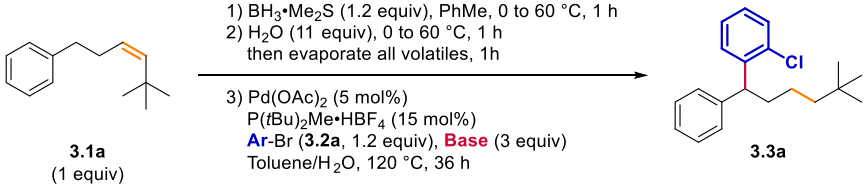


Entry	Temperature	Yield (%)[a]	rr[b]
1	90	32	>99:1
2	100	65	>99:1
3	120	78	>99:1
4[c]	120	71	>99:1

[a] Yield of **3.3a** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis; [c] Xylenes were used instead of toluene.

When comparing different bases (Table **3.2**) to the initial conditions with caesium carbonate (entry **1**), we only obtained 50% of the product with potassium phosphate (entry **2**). Sodium hydroxide gave only 24% of the product (entry **3**), but switching the alkali counterion to potassium increased the yield (entry **4**). Barium hydroxide showed no improvement (entry **5**), whereas the reactions with *tert*-butoxide bases were sluggish (entry **6**, **7**), and triethylamine completely shut down the reaction (entry **8**). Potassium acetate gave only 8% (entry **9**) and potassium carbonate gave a modest 54% yield (entry **10**). Even though potassium hydroxide gave a 1% higher yield, we decided to use the milder caesium carbonate.

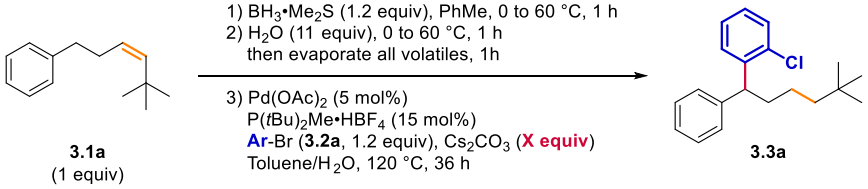
Table 3.2: Screening of the base.



Entry	Base	Yield (%)[a]	rr[b]
1	Cs_2CO_3	78	>99:1
2	K_3PO_4	50	>99:1
3	NaOH	24	>99:1
4	KOH	79	>99:1
5	$Ba(OH)_2{\cdot}8H_2O$	51	>99:1
6	NaO*t*Bu	16	>99:1
7	KO*t*Bu	41	>99:1
8	Et_3N	-	-
9	KOAc	8	>99:1
10	K_2CO_3	54	>99:1

[a] Yield of **3.3a** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis.

Table 3.3: Screening of the amount of the base.



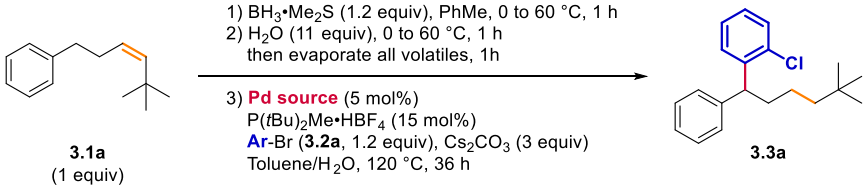
Entry	Amount of Base	Yield (%)[a]	rr[b]
1	1.0 equiv	33	>99:1
2	1.5 equiv	54	>99:1
3	2.0 equiv	68	>99:1
4	2.5 equiv	75	>99:1
5	3.0 equiv	78	>99:1

[a] Yield of **3.3a** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis.

We also checked the necessary equivalents of base (Table **3.3**). Only 33% of the product was obtained when just one equivalent was used (entry **1**), which could be raised to 54% with 1.5 equivalents (entry **2**). Further increasing the amount of the base also increased the yield (entry **3**, **4**), and three equivalents of caesium carbonate gave the best result (entry **5**).

We then tested different palladium sources to see if we could further increase the yield (Table **3.4**). Moving from palladium acetate (entry **1**) to palladium trifluoroacetate (entry **2**) gave a slight increase in yield. Lower yields were obtained with palladium pivalate and acetylacetonate (entry **3**, **4**), whereas as comparable outcome to palladium acetate was observed with palladium chloride (entry **5**). Additionally, ligated palladium chloride species led to a decrease of the yield (entry **6**, **7**) which was less pronounced for the palladium (π-cinnamyl) chloride dimer (entry **8**). Interestingly, significantly lower yields were also observed when $Pd_2(dba_3)\cdot CHCl_3$ was used (entry **9**).

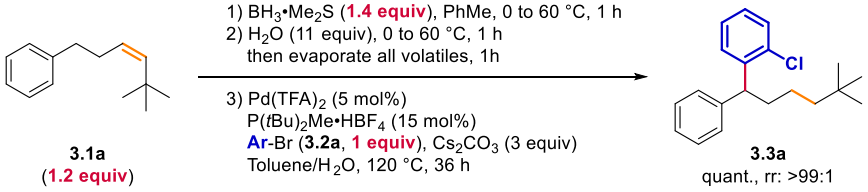
Table 3.4: Screening of the palladium source.



Entry	Pd source	Yield (%)[a]	rr[b]
1	$Pd(OAc)_2$	78	>99:1
2	$Pd(TFA)_2$	82	>99:1
3	$Pd(OPiv)_2$	62	>99:1
4	$Pd(acac)_2$	56	>99:1
5	$PdCl_2$	76	>99:1
6	$PdCl_2(MeCN)_2$	17	>99:1
7	$PdCl_2(cod)$	10	-
8	$[PdCl(\pi\text{-cin})]_2$	65	>99:1
9	$Pd_2(dba)_3\cdot CHCl_3$ (2.5 mol%)	37	>99:1

[a] Yield of **3.3a** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis.

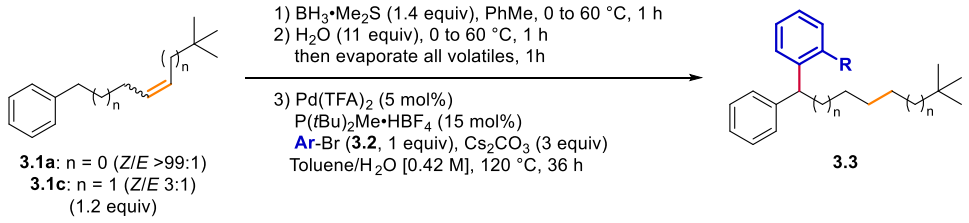
As the reaction seemed to have reached a maximum yield of 82%, we decided to inverse the role of the limiting partner. Thus, we engaged a slight excess of the alkene and one equivalent of the electrophile (Scheme **3.5**). Satisfyingly, the product **3.3a** was obtained exclusively and in quantitative yield with these conditions.



Scheme 3.5: Electrophile as limiting coupling partner; Yield of **3.3a** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis.

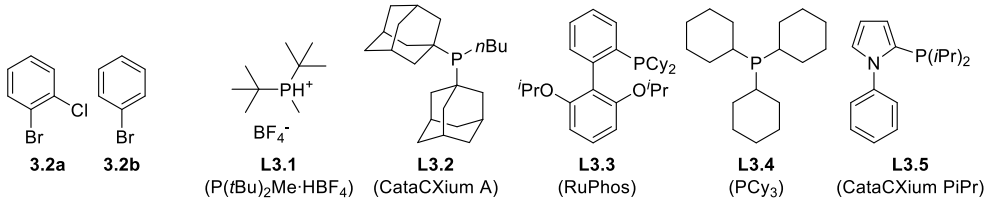
Since none of the aforementioned reaction parameters had an impact on the regioselectivity, we wanted to validate the necessity of the *ortho*-substituent on the electrophile (Table **3.5**). Somewhat unexpectedly due to the previous investigations (*see also* Section **2.2.2**), an excellent yield and regioselectivity of 96:4 was obtained when using simple bromobenzene (**3.2b**, entry **1**). A big difference of the outcome was observed when different ligands were tested (entry **2**-**5**), confirming the need of a small and electron rich ligand.[220] Notably, CataCXium PiPr (**L3.5**), which gave optimal selectivity in previous migratory Negishi cross couplings[162–166] gave only a 21:79 ratio supressing the migration (entry **5**), thus highlighting the different behaviour of the catalyst between the different types of migratory cross-couplings. Unfortunately, a non-negligible drop in regioselectivity was observed when the alkyl chain was elongated by just one methylene unit on both sides of the alkene (**3.1c**, entry **6**). Apparently, the steric bulk of the *tert*-butyl group on alkene **3.1a** is sufficiently close to push the chain-walk to the benzylic position, but this effect weakens with a longer chain (**3.1c**). However, the loss in regioselectivity could be recovered when the *ortho*-substituted aryl bromide **3.2a** was used, furnishing the exclusive 1,1-diarylalkane product **3.3c** in high yield and excellent regioselectivity (entry **7**).

Table 3.5: Testing the influence of the ligand and *ortho*-substituent.



Entry	Variation from conditions	ArBr	Alkene	Yield (%)[a]	rr[b]
1	-	**3.2b**	**3.1a**	96	96:4
2	ligand: CataCXium A (**L3.2**)	**3.2b**	**3.1a**	9	7:93
3	ligand: RuPhos (**L3.3**)	**3.2b**	**3.1a**	27	78:22
4	ligand: PCy_3 (**L3.4**)	**3.2b**	**3.1a**	18	49:51
5	ligand: CataCXium PiPr (**L3.5**)	**3.2b**	**3.1a**	10	21:79
6	-	**3.2b**	**3.1c**	77	84:16
7	-	**3.2a**	**3.1c**	70	>99:1

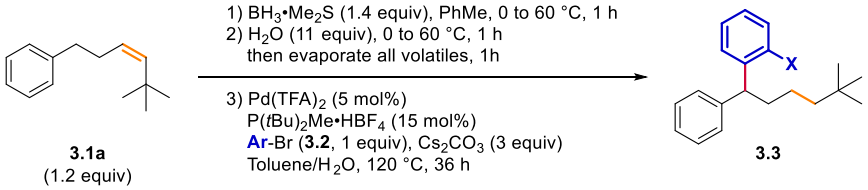
[a] Yield of **3.3** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis; [c] Yield of the isolated product.



Finally, other *ortho*-dihalobenzenes were tested (Table **3.6**). The reaction still proceeds efficiently with *ortho*-dichlorobenzene (**3.2c**, entry **1**), but would presumably lead to a mixture of regioisomers if further substituted. Additionally, a drop in reactivity was observed with

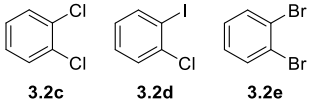
1-chloro-2-iodobenzene (**3.2d**, entry **2**) which was even more pronounced with *ortho*-dibromobenzene (**3.2e**, entry **3**).

Table 3.6: Test-reactions with different electrophiles.



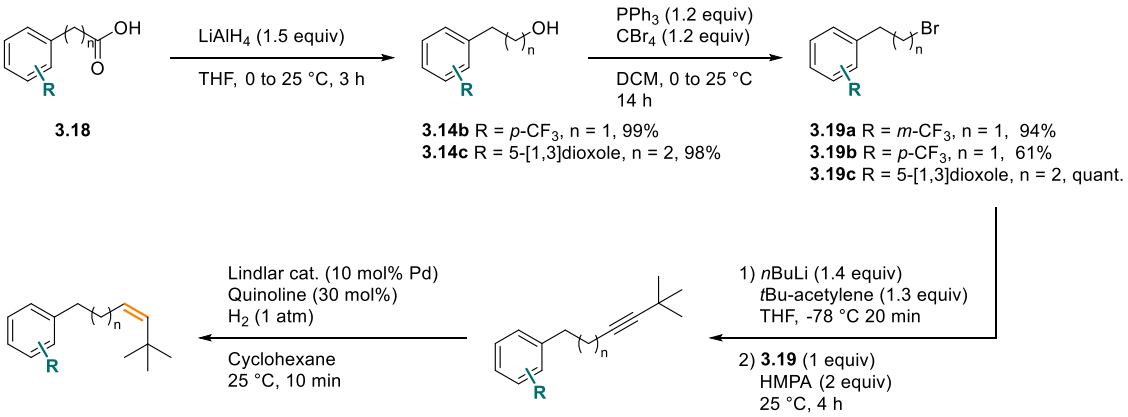
Entry	ArBr	Yield (%)[a]	rr[b]
1	**3.2c**	91	>99:1
2	**3.2d**	74	>99:1
3	**3.2e**	37	>99:1

[a] Yield of **3.3** determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis.



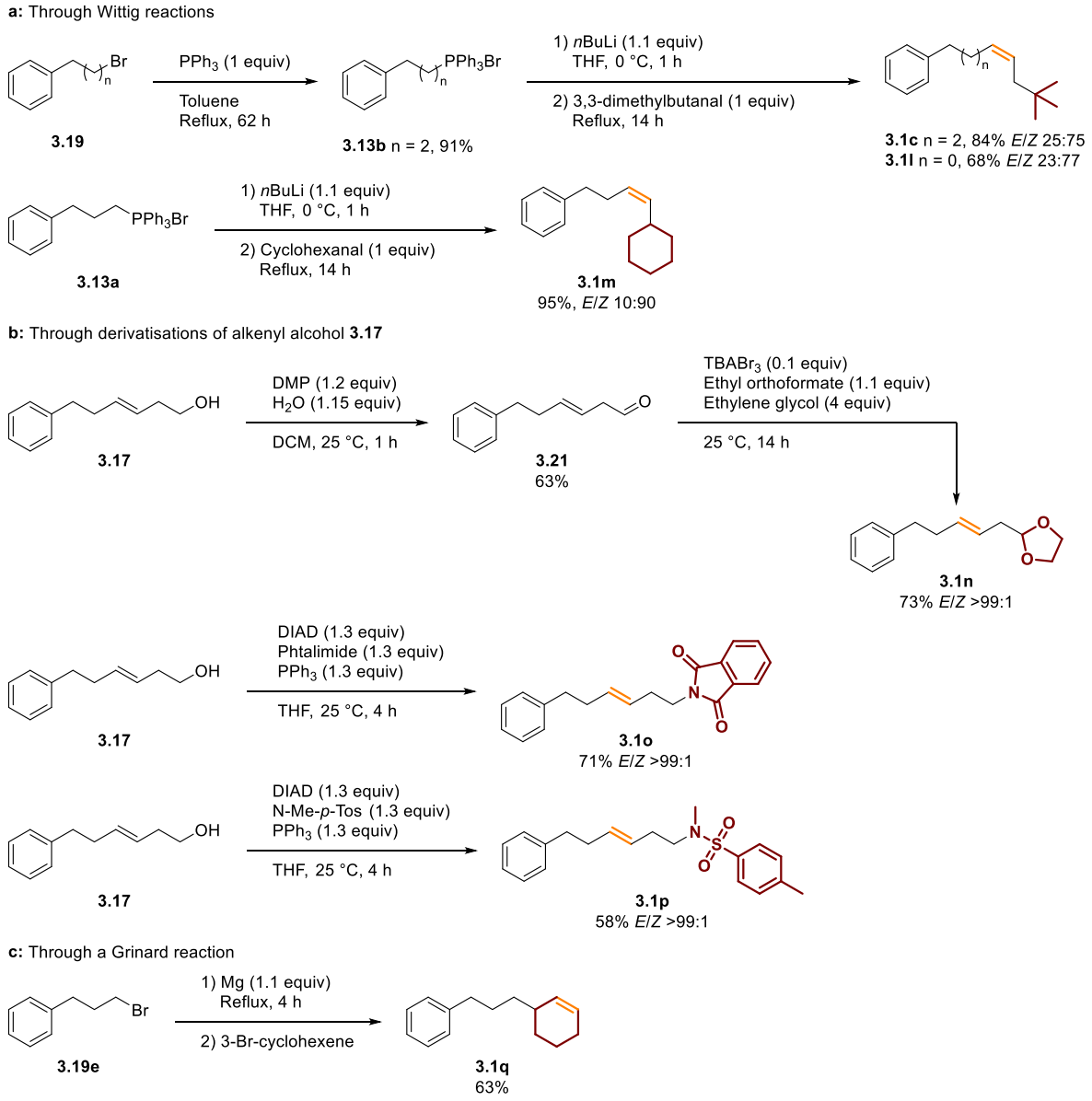
3.2.3. Scope and Limitations

With optimal reaction conditions in hand, we turned our attention to investigate the generality of our reaction. Thus, various alkenyl arenes were synthesized with a variety of substituents at different positions on the aryl moiety. A general approach starting from carboxylic acids, or commercial intermediates, is shown in Scheme **3.6**. The carboxylic acids **3.18** are reduced to the alcohols **3.14** which are then substituted in an Appel reaction yielding the alkyl bromides **3.19**. A nucleophilic substitution with lithiated *tert*-butylacetylene gives the alkynes **3.20**, which are then partially reduced to the predominantly (*Z*)-alkenes **3.1d** - **3.1k** using the Lindlar catalyst and hydrogen gas with modest *E*/*Z* ratios.



Scheme 3.6: Synthesis of the different alkenyl arenes **3.1d** – **3.1k**.

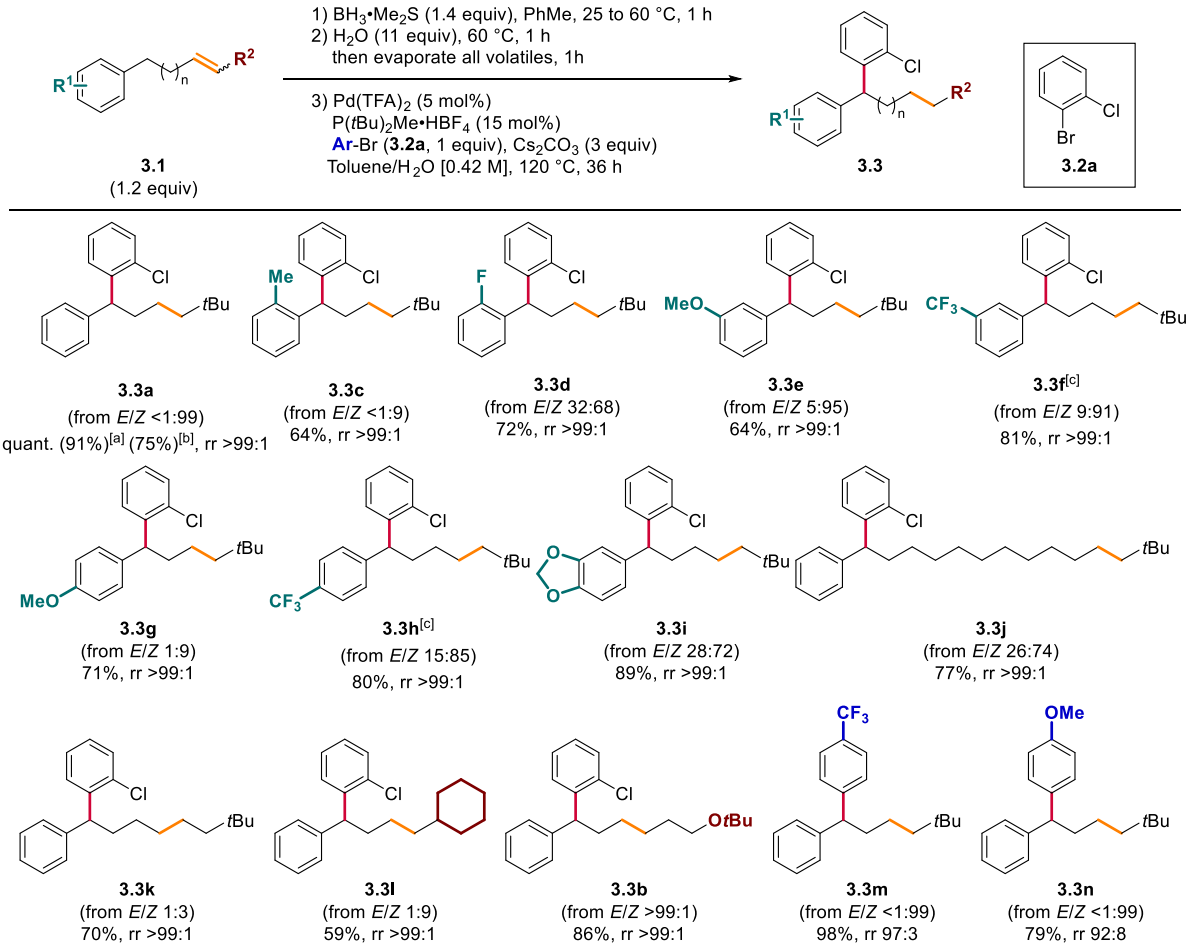
Further alkenyl arenes with longer alkyl chains **3.1c** and **3.1l**, or different blocking group **3.1m** from the model substrate **3.1a**, were obtained through a Wittig reaction (Scheme **3.7a**). Substrates with different functional groups **3.1n** - **3.1p** that could efficiently block the chain-walking, were obtained through derivatisation of the previously described alkenyl alcohol **3.17** (*see also* Scheme **3.3**) by either a Dess-Martin oxidation and successive acetalisation of the obtained aldehyde **3.21**, or by a Mitsunobu reaction (Scheme **3.7b**). Finally a cyclic alkene **3.1q** was prepared by a Grignard reaction (Scheme **3.7c**) to see if our reaction proceeds efficiently when a *tertiary* carbon is on the path to the benzylic position.



Scheme 3.7: Synthesis of alkenyl arenes **3.1c**, **3.1l** – **3.1q**.

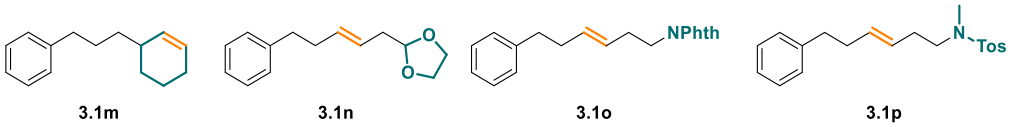
We then evaluated the scope of the alkenes with 1-bromo-2-chlorobenzene (**3.2a**) as the electrophile (Scheme **3.8**). Both, electron-donating and electron-withdrawing substituents, were well tolerated in *ortho*- (**3.3c**, **3.3d**), *meta*- (**3.3e**, **3.3f**) and *para*-position (**3.3g**, **3.3h**) as well as a disubstituted 1,2-methylenedioxybenzene (**3.3i**). Importantly, the initial geometry of the alkene had no noticeable impact as pure (*Z*)- (**3.3a**, **3.3c**, **3.3m**, **3.3n**), (*E*)-alkenes (**3.3b**) or

E/*Z* mixtures (**3.3d** - **3.3l**) underwent hydroboration and successive migratory SMC efficiently and selectively. Remarkably, excellent results were obtained when a longer-chain alkene was used as starting material, furnishing product **3.3j** in high yield and perfect regioselectivity with a migratory distance of ten positions with respect to the initial alkene site. The reaction also proceeds with a cyclohexyl (**3.3l**) or a *tert*-butyl ether (**3.3b**) as blocking group, for the latter enabling further functional group transformation at this end of the alkyl chain. We additionally demonstrated the practicability of our protocol by performing the reaction on a ten-fold larger scale (5.0 mmol) and without need of using the glovebox for the synthesis of the model compound **3.3a**. The reaction proceeded efficiently with excellent regioselectivity and a slightly lower yield mainly due to difficult purification. Furthermore, the reaction also performed well yielding 75% of **3.3a** when the amount of borane was decreased to 0.45 equivalents, thus leading to the formation of tri-*sec*-alkylborane. It is noteworthy to mention that our system is able to react with the three *secondary* alkyl moieties of this trialkylborane, which is to date unmet in a general protocol. [200–203]



Scheme 3.8: Scope of alkenes of the migratory SMC. The geometry of the initial alkenes is indicated in parenthesis, and the initial positions of the alkenes is highlighted in orange. Scale of the reactions: 0.50 mmol. Yields refer to the isolated product. Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis of the crude reaction mixture. [a] Performed on a 5.0 mmol scale; [b] 0.45 equiv of BH_3·DMS used; [c] Isolated as the C-H arylation products (**3.25a**, **3.25b**), yield over two steps, see also Scheme **3.11b**.

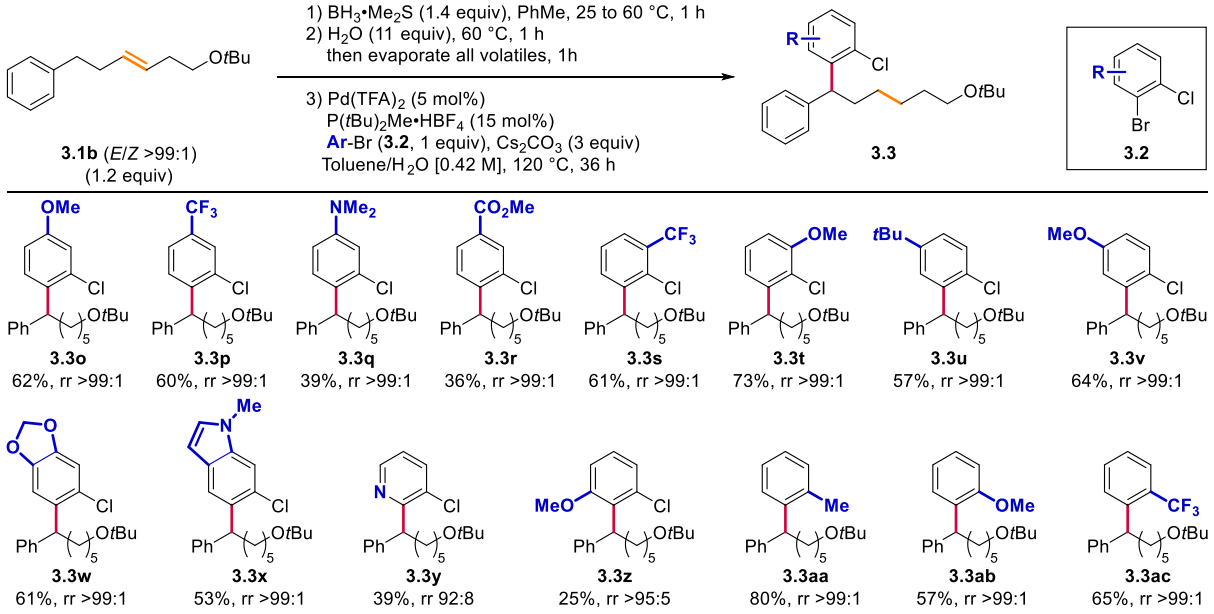
Additionally, very high regioselectivity and yield were obtained without *ortho*-substituent on the aryl bromide when the terminal position was blocked with a bulky *tert*-butyl group and the migration distance was short (**3.3m**, **3.3n**). Unfortunately, the reaction did not tolerate some of the blocking groups (Figure **3.2**). The reaction furnished only isomerised alkene when **3.1m** was engaged, presumably due to easy decoordination of the palladium-hydride intermediate from the *in situ* formed trisubstituted alkene, and the reaction with **3.1n** completely decomposed the substrate. Somewhat surprisingly, the presence of a nitrogen seemed to inhibit the hydroboration as the starting materials **3.1o** and **3.1p** were mainly recovered from the reaction mixture.



3.1m 3.1n 3.1o 3.1p

Figure 3.2: Unsuccessful examples of alkenes.

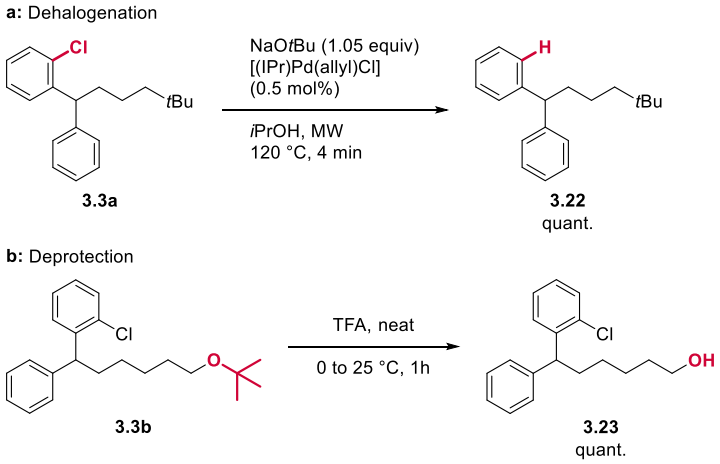
We then explored the scope of the electrophiles with the *tert*-butyl ether alkene **3.1b** (Scheme **3.9**). We first evaluated various substituted 1-bromo-2-chlorobenzenes. Electron donating and electron withdrawing substituents in *para*- (**3.3o** - **3.3r**) and both *meta*-positions (**3.3s** - **3.3v**) with respect to the formed bond were well tolerated. Furthermore, trisubstituted as well as heteroaromatic electrophiles were also tolerated as shown with 1,2-methylenedioxybenzene (**3.3w**), indole (**3.3x**) and pyridine (**3.3y**) although a slight drop in regioselectivity was observed with the latter. An additional *ortho*-substituent furnished only 25% of **3.3z**, presumably due to the increased steric hindrance. Notably, as also previously observed (*see also* Table **2.19**), the *ortho*-chloride can also be replaced with a methyl (**3.3aa**), a methoxy (**3.3ab**) of a trifluoromethyl group (**3.3ac**) to obtain *ortho*-substituted products in high yield and perfect selectivity.



Scheme 3.9: Scope of electrophiles of the migratory SMC. The geometry of the initial alkenes is indicated in parenthesis, and the initial positions of the alkenes is highlighted in orange. Scale of the reactions: 0.50 mmol. Yields refer to the isolated product. Regioisomeric ratio (rr) of benzylic/sum of other regioisomers were determined by GCMS analysis of the crude reaction mixture.

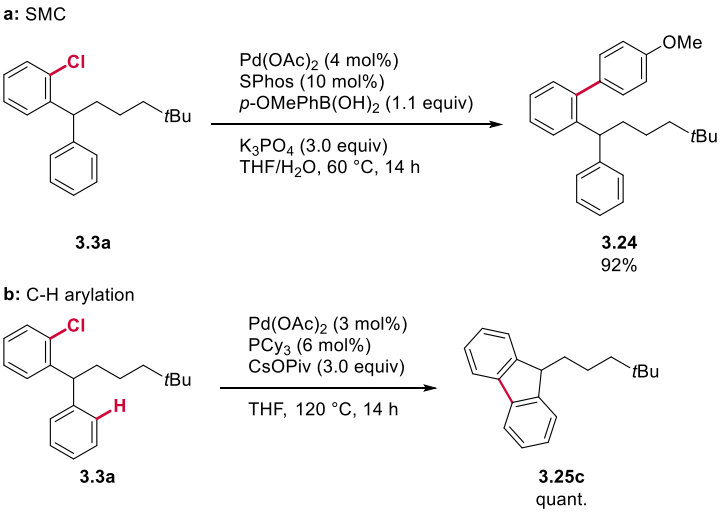
3.2.4. Deprotection and Postfunctionalisation

We then further transformed the products to demonstrate the versatility of the products obtainable with our reaction. First, the *ortho*-chloride substituent, which we used as a removable directing group for the majority of the examples, was efficiently cleaved by palladium-catalysed dehalogenation to obtain **3.22** in a quantitative yield (Scheme **3.10a**).[221] It should be noted that traditional hydrogenation with palladium on charcoal and hydrogen gas did not furnish **3.22**. The alcohol was also rapidly deprotected by simply stirring **3.3b** in trifluoroacetic acid to obtain the terminal free alcohol **3.23** (Scheme **3.10b**). Milder conditions for the cleavage of *tert*-butyl ethers also exist,[222] if labile functional group were to be present on the substrate.



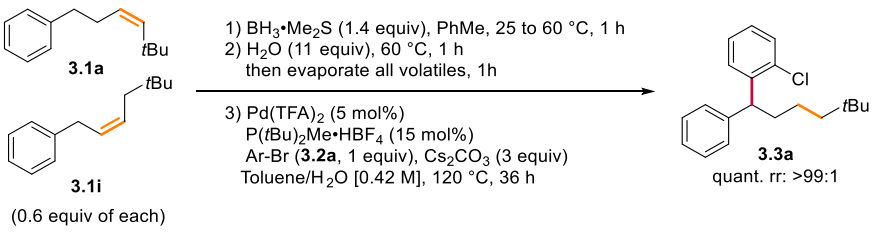
Scheme 3.10: Removal of the directing and protecting groups.

The aryl-chloride was also employed to perform further transformations as demonstrated by the SMC with *para*-anisylboronic acid yielding the biphenyl **3.24** in excellent yield (Scheme **3.11a**),[223] or by the C-H arylation to obtain the 9-*n*-alkyl-fluorene **3.25** (Scheme **3.11b**).[224] Two other fluorenes (**3.25a**, **3.25b**, Scheme **3.8**) were also synthesized from the corresponding migratory SMC products for easier purification.



Scheme 3.11: SMC and C-H arylation with the *ortho*-Chloride.

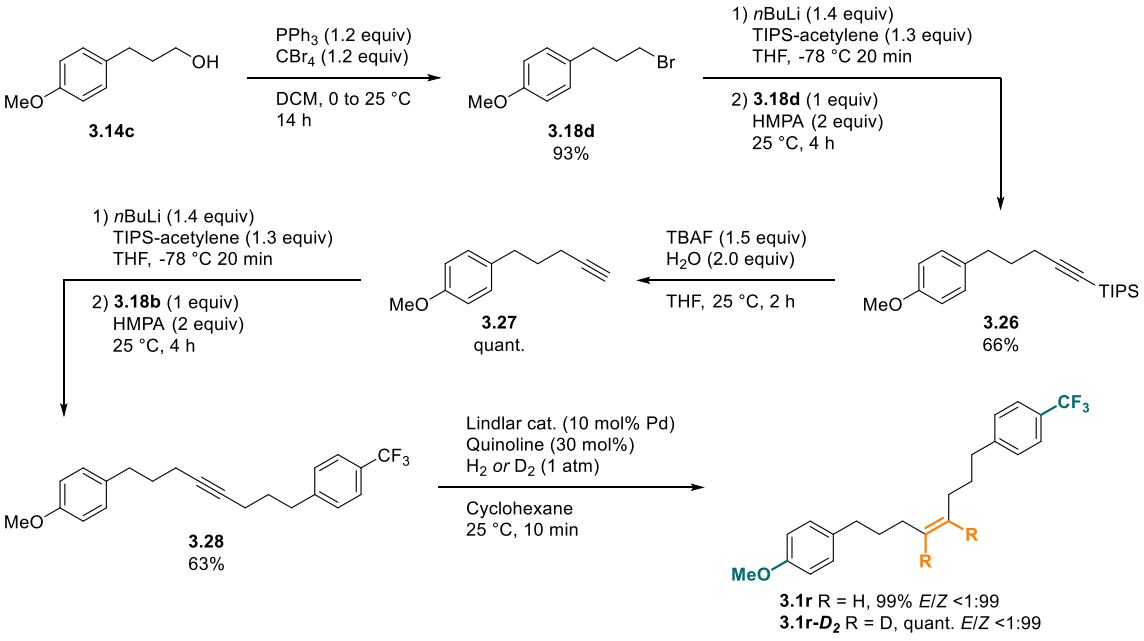
One of the most powerful feature of migratory functionalisation is their ability to transform regio- and stereoisomers into one single product (*see also* Section **1.3**). Besides already shown for the convergence of (*E*)- and (*Z*)-alkenes (*see also* Scheme **3.8**) we further demonstrated this by engaging a one-to-one mixture of two positional isomers **3.1a** and **3.1i**, which, as expected, furnished **3.3a** in quantitative yield and perfect regioselectivity (Scheme **3.12**).



Scheme 3.12: Regioconvergent coupling through migratory SMC.

3.2.5. Mechanistic Considerations.

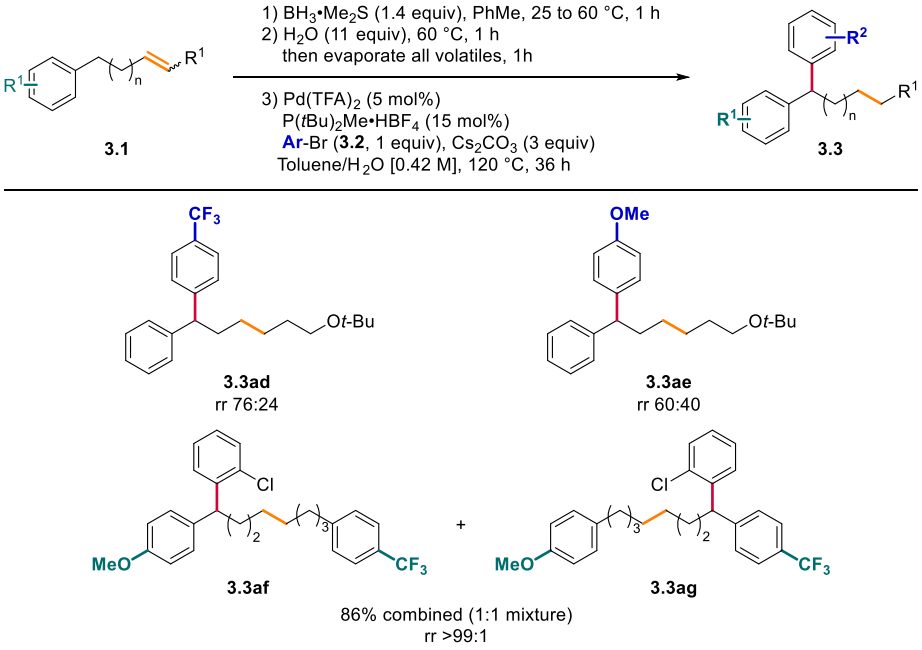
We then performed a mechanistic study to gain additional insights in the factors influencing the regioselectivity and mechanism. We started with the synthesis of an alkenyl arene (**3.1r**) bearing at each end of the alkyl chain either an electron rich or an electron poor aryl moiety at the same distance from the alkene, with a similar approach to the one previously used (Scheme **3.13**). The analogous compound was then also prepared with deuterium atoms on the olefin (**3.1r-*D*$_2$**) for an isotopic labelling experiment.



Scheme 3.13: Synthesis of alkenyl arenes **3.1r** and **3.1r-*D*$_2$**.

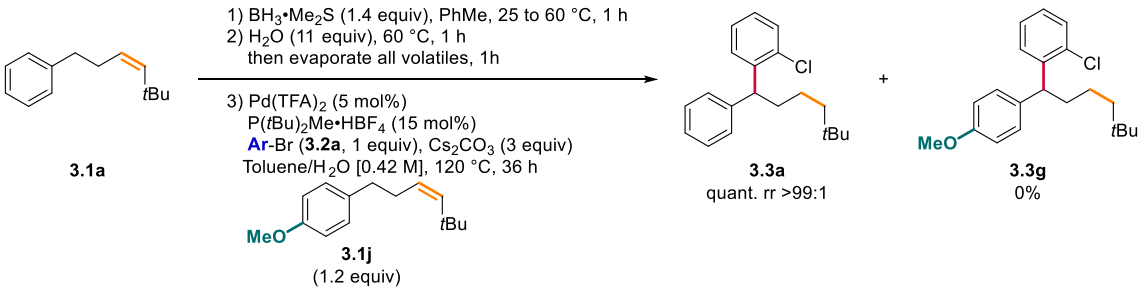
To investigate the electronic properties of the electrophilic partner, we performed the migratory SMC reaction with *para*-bromobenzotrifluoride and *para*-bromoanisole (Scheme **3.14**). An electron poor electrophile (**3.3ad**) provided a slightly better selectivity than the electron rich electrophile (**3.3ae**). Additionally, we already showed that excellent regioselectivity was achieved regardless of the electronic nature of the *ortho*-substituent

(**3.3aa** - **3.3ac**, Scheme **3.9**). Furthermore, a statistical one-to-one ratio of products **3.3af** and **3.3ag** was observed for alkene **3.1r**, clearly indicating that the aryl group on the alkylboronic acid partner has no influence on the selectivity (Scheme **3.14**). These findings indicate that steric factors have a more pronounced influence than the electronic effects, similar to the migratory Negishi cross-coupling.[166]



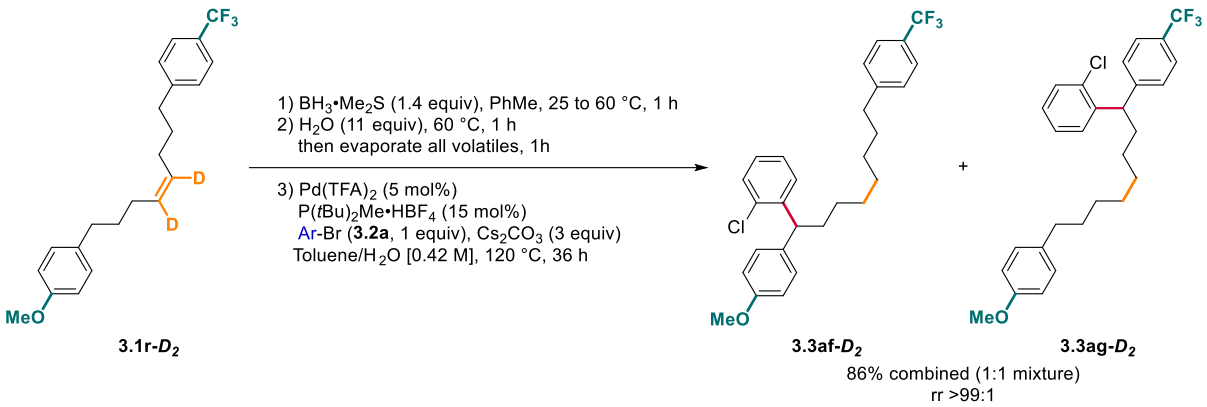
Scheme 3.14: Influence of the substituents on both partners on the regioselectivity.

Next, we wanted to determine whether the chain-walk proceeds through a non-dissociative pathway or if the transient palladium-hydride can dissociate from the transient alkene. Therefore, we performed a crossover experiment by simply adding olefin **3.1j** to the reaction mixture after the hydroboration of **3.1a** (Scheme **3.15**). The complete absence of **3.3g** and quantitative yield for **3.3a** is clearly indicative for a non-dissociative chain-walk process (*see also* Section **1.3.2**), similar to other migratory cross-couplings investigated by the Baudoin group.[157–160,162–166]



Scheme 3.15: Crossover experiment.

Finally the deuterated alkene **3.1r-*D*$_2$** was engaged in the migratory SMC reaction to elucidate if deuterium scrambling occurs along the alkyl chain, and to what positions (Scheme **3.16**). As for the non-deuterated analogue, a statistical mixture of both possible 1.1-diarylalkane products **3.3af-*D*$_2$** and **3.3ag-*D*$_2$** was obtained.



Scheme 3.16: Isotopic labelling experiment.

Remarkably, no deuterium was observed in any of the benzylic positions (**a**, **d**, Figure **3.3**), indicating that the catalyst migration to the benzylic position is irreversible, which is consistent with the observation that the electronic properties of the benzylic position does not influence the regioselectivity (*see also* Scheme **3.14**). Additionally, only little incorporation of deuterium was measured in α-position (**b**) of the newly formed bond (~5%), whereas all the remaining methylene groups bear to some extend deuterium atoms. These results show that a reversible and statistical chain-walk occurs until the catalyst reaches the benzylic position, where the benzylpalladium intermediate acts as a thermodynamic sink within the migration pathway and thus furnishing the products in excellent regioselectivity.

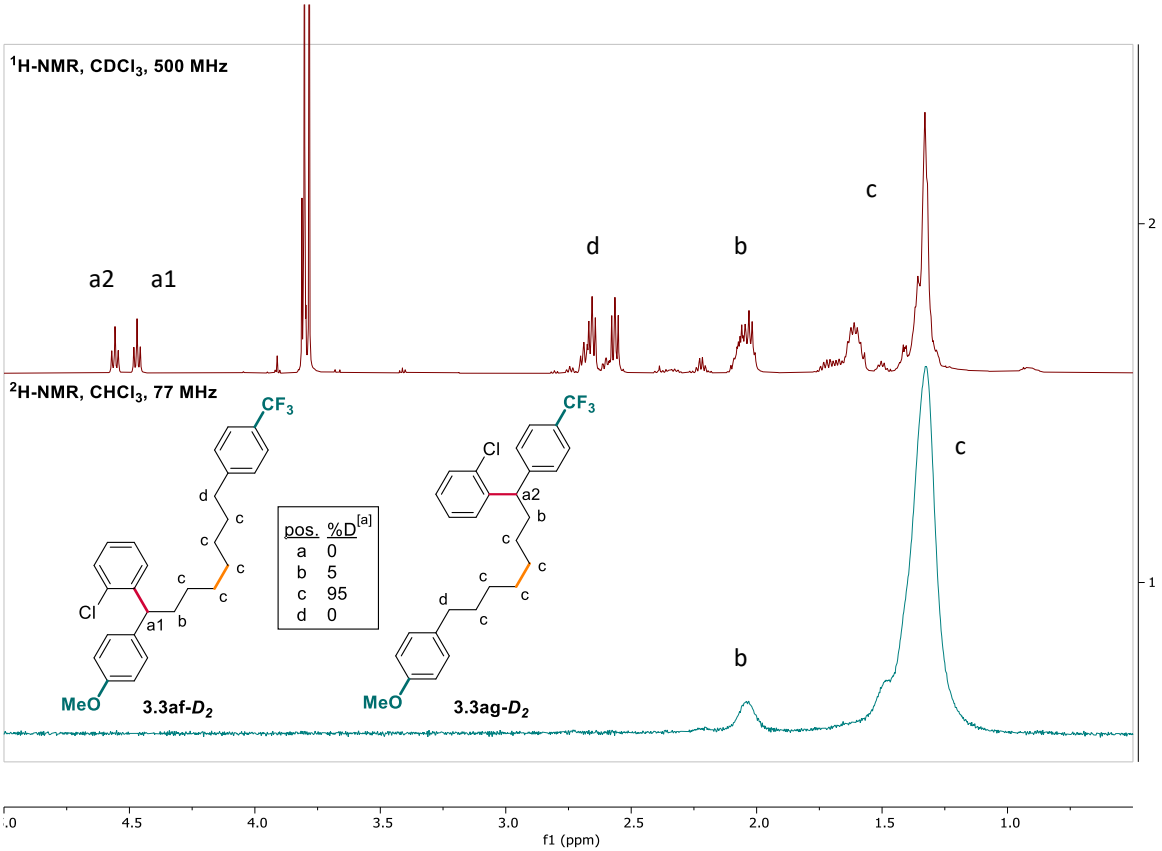
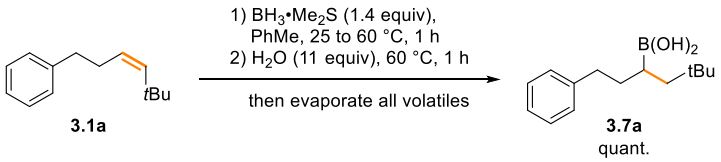


Figure 3.3: Stacked ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{2}H-NMR ($CHCl_3$, 77MHz) spectra of **3.3af-*D*$_2$** and **3.3ag-*D*$_2$**.

To identify the generated alkylboron species, we simply engaged the alkene **3.1a** to hydroboration under the same conditions of the whole sequence and stopped after the evaporation of the volatiles (Scheme **3.17**).



Scheme 3.17: Interrupted reaction sequence for the determination of the organoborane species.

A clear and sharp peak at 19.49 ppm was observed in the ^{11}B-NMR spectrum of **3.7a**, which is in the range of organoboronic acids (~15 – 35 ppm), compared to organoborinic acids (~40 – 60 ppm) and triorganoboranes (~80 – 90 ppm).[225] Additionally, the absence of a second peak slightly upfield, despite using deuterated water as solvent, is indicative for the absence of organoboroxine, as this specie would partially be hydrolysed to the boronic acid analogue in presence of water. Thus we concluded, that the *sec*-alkylboronic acid species **3.7** is generated and active in our reaction.

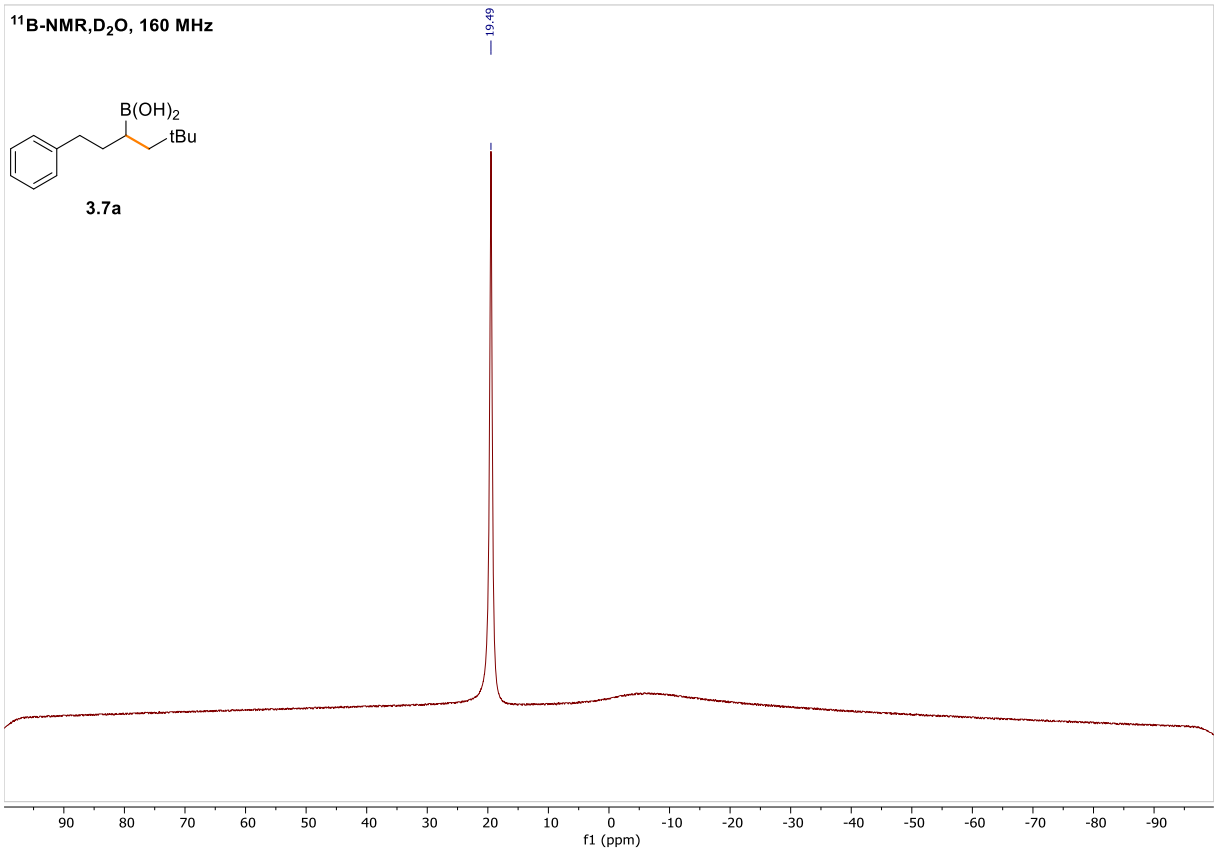
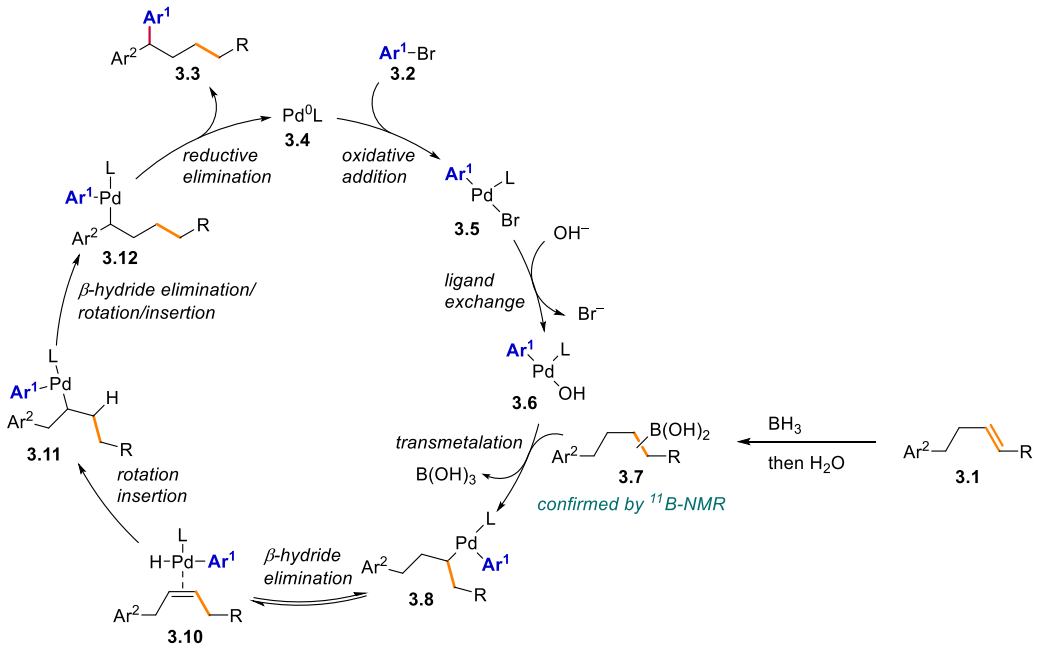


Figure 3.4: ^{11}B-NMR (D_2O, 160 MHz) of **3.7a**.

With the combined results in hand, we confirm the initialy proposed catalytic cycle for the current migratory SMC (Scheme **3.18**). Oxidative addition of the electrophile **3.2** to the *in situ* generated Pd^0 catalyst **3.4** and successive ligand exchange gives hydroxy-palladium species **3.6**. Transmetalation with the *sec*-alkylboronic acid **3.7** obtained by hydroboration of the alkene **3.1** yields the intermediate **3.8**. A small and electron rich ligand **L** as well as an

ortho-substituted **Ar¹** group significantly increases the activation barrier of the reductive elimination as proposed by DFT calculations for related cross-couplings,[157,158] and thus the alkylpalladium species **3.8** undergoes chain-walking through a series of non-dissociative β-hydride elimination/π-bond rotation/insertion steps until the catalyst eventually reaches a benzylic position **3.12**. Reductive elimination at this site furnishes the benzylic cross-coupling product **3.3** at the expense of other regioisomers, while regenerating the Pd^0 catalyst **3.4**.



Scheme 3.18: Proposed catalytic cycle. The generation of the active Pd^0 was omitted for clarity.

A closer look at the different energies for the steps of the final catalyst-migration, represented in qualitative energy profile format based on DFT calculations for related cross-couplings,[157,158] is displayed in Figure **3.5**. The chain-walk of the catalyst towards the benzylic position **3.12** (blue path) is energetically favoured compared to the two unwanted side reaction leading to regioisomer **3.9** and isomerised starting material **3.1'** (red paths). The reductive elimination at the benzylic position is favoured over the back-migration, and thus a perfect regioselectivity for the product **3.3** is achieved.

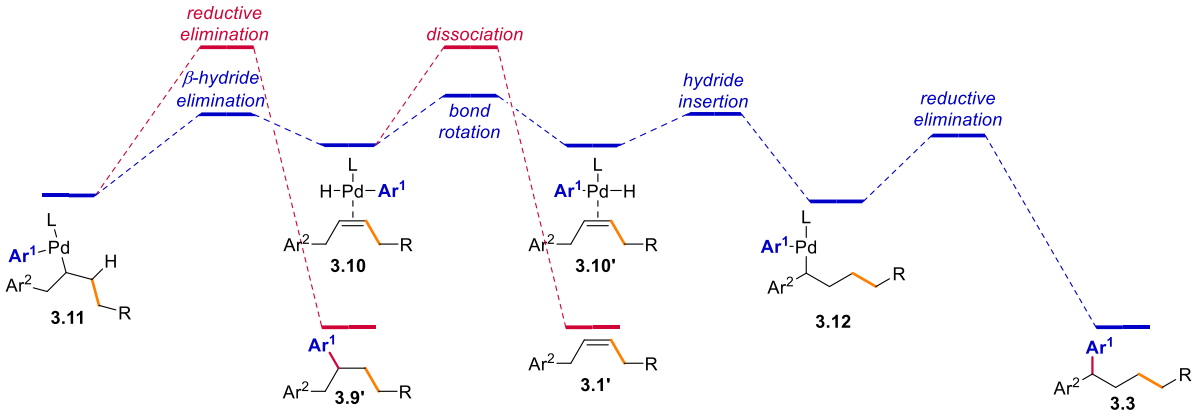


Figure 3.5: Qualitative energy profile on the selectivity of the site of reductive elimination.

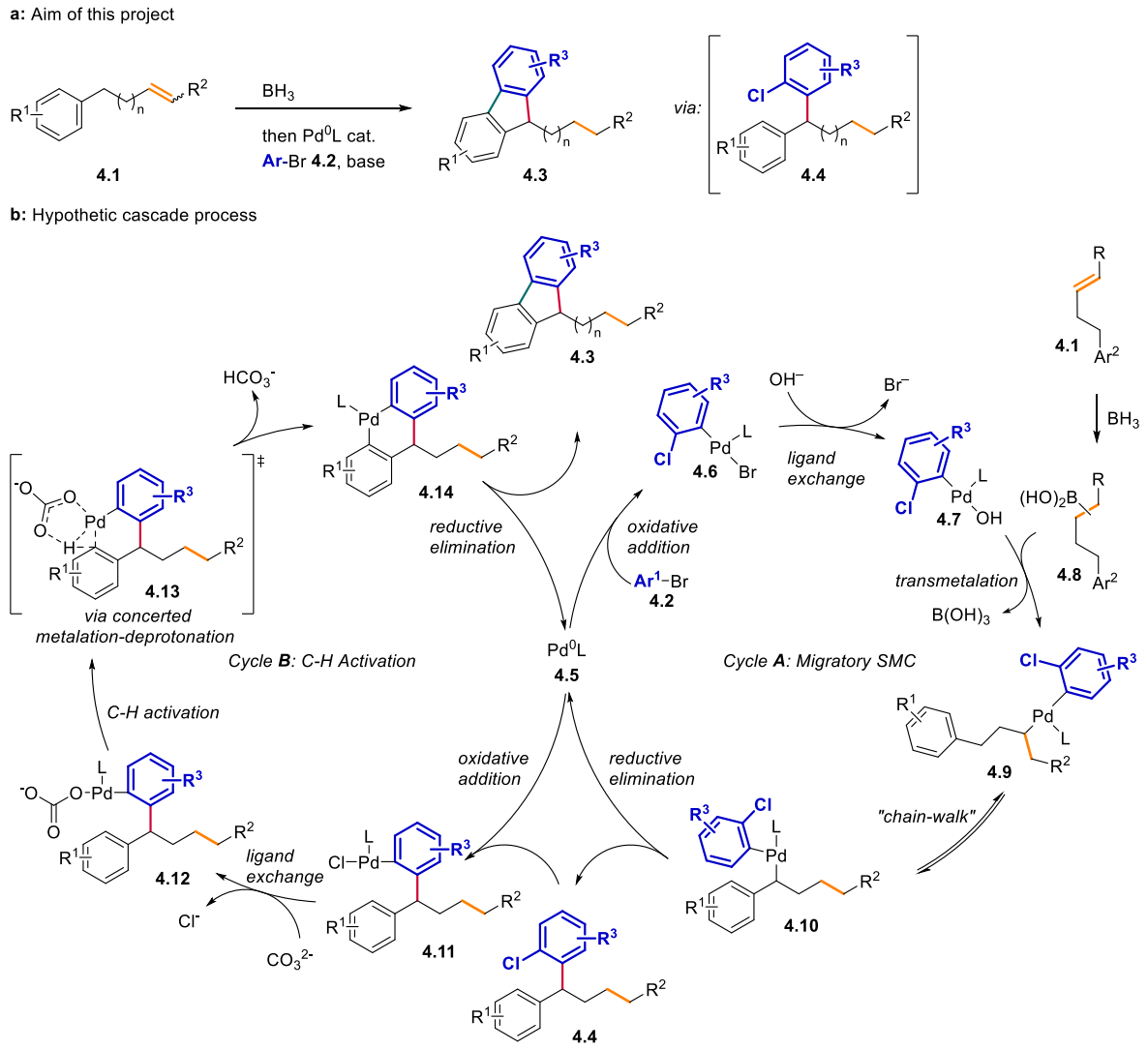
3.3. Conclusion

In summary, we have developed the first palladium-catalysed migratory SMC of *sec*-alkylboronic acid, obtained by hydroboration of alkenes, and bromoarenes for the synthesis of a variety of 1,1-diarylalkanes. The developed one-pot procedure for the generation of *sec*-alkylboronic acids and their subsequent migratory SMC avoids the often-difficult purification and isolation of these intermediates. Excellent regioselectivity and high yields are achieved by employing a small, electron rich ligand and *ortho*-substituted electrophiles. Particularly, using an *ortho*-chloro substituent on the electrophile, or a protected alcohol at the other end of the alkyl chain of the alkenyl arene, allowed for a broad diversity of substitution patterns and postfunctionalisations. The regioconvergent nature as well as a long-range example further demonstrated the power of this palladium-catalysed migratory Suzuki-Miyaura cross-coupling. Furthermore, a mechanistic study indicates a partially reversible non-dissociative catalyst migration along the alkyl chain until the stabilised benzylic position, where reductive elimination is facile.

4. Benzylic-Selective Palladium-Catalysed Migratory Suzuki-Miyaura Cross-Coupling – C(sp^2)-H Activation Cascade

4.1. Design Plan

The products (**4.4**) obtained through the one-pot alkene hydroboration/migratory palladium-catalysed SMC which is described in Chapter **3** are ideal precursors for the synthesis of 9-*n*-alkyl-fluorenes (**4.3**) through a C(sp^2)-H activation (*see also* Scheme **3.11**). As the reaction conditions used for the migratory SMC are similar for the two reactions, we envisioned a possible cascade process combining the one-pot alkene hydroboration/migratory palladium-catalysed SMC and the C(sp^2)-H activation as shown in Scheme **4.1a**.

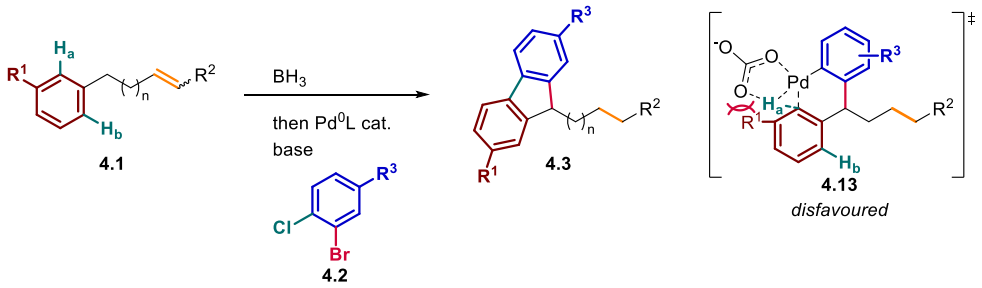


Scheme 4.1: Preparation of 9-*n*-alkyl-fluorene (**4.3**) through a migratory SMC/C(sp^2)-H activation cascade.

A hypothetical working principle is depicted in Scheme **4.1b**. The 1,1-diarylalkane product **4.4** is obtained in the same way as elaborated previously in Scheme **3.18** (Cycle **A**). In a second

catalytic cycle, oxidative addition of the obtained migratory SMC product **4.4** with the regenerated Pd^0 catalyst **4.5** furnishes intermediate **4.11**, which then undergoes ligand exchange with a carbonate to yield **4.12**. This intermediate then undergoes C-H activation through a concerted metalation-deprotonation (CMD) mechanism, which yields the palladacycle **4.14**. Reductive elimination furnishes the 9-*n*-alkyl-fluorene product **4.3** and regenerates the catalyst.

Employing substituted 1-bromo-2-chlorobenzene (**4.2**) would furnish the products with predictable substitution pattern on the fluorene moiety (Scheme **4.2**) as the oxidative addition of a Pd^0 catalyst is kinetically favoured for the bromide compared to chloride. Thus, the bond formed through the migratory SMC would take place at the *ipso*-position of the bromide, and the C-H activation at the *ipso*-position of the chloride. Only a *meta*-substituent on the aryl of the starting alkene (**R^1**, **4.1**) could possibly lead to selectivity issues, but the steric hindrance (**4.13**) would presumably lead to the product **4.4** where the substituent is in *para*-positions of the formed bond.



Scheme 4.2: Substitution pattern is predictable.

However, a major challenge is expected for the two distinct ligand exchange steps (Scheme **4.1**). The developed migratory SMC employs a mixture of toluene and water as a solvent system, and thus the carbonate base is predominantly solvated in the aqueous phase. This does not only dramatically decrease the concentration of the carbonate present in the organic phase, but also means that hydroxide ions will be competing with the carbonate.

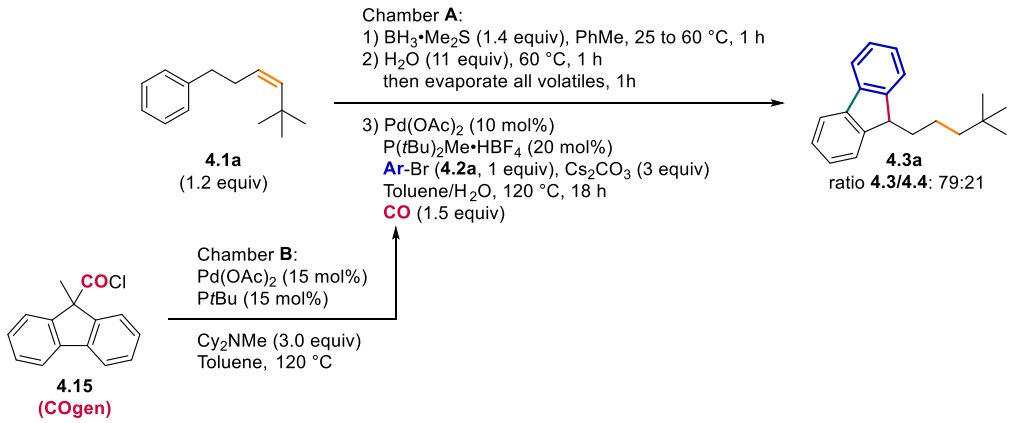
The products obtainable through the proposed cascade process, i.e. methylene-bridged polyarenes, have become an important class of compounds in materials science such as light-emitting diodes or semiconductor,[226–228] among which, fluorene is the most representative structural motif.[229–233] Thus, the proposed approach would furnish highly valuable products in a single sequence starting from cheap and readily available substrates.

4.2. Results & Discussion

4.2.1. Preliminary Test-Reactions

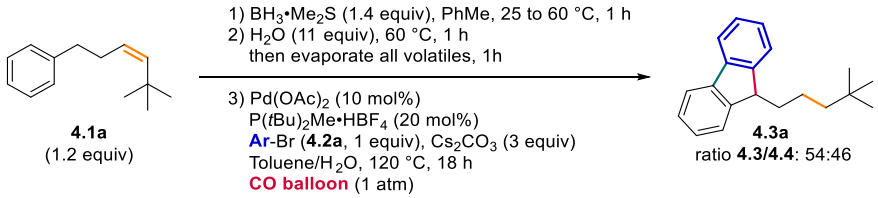
We first encountered the formation of 9-*n*-alkyl-fluorenes (**4.3**) during our investigation of the migratory SMC in presence of carbon monoxide. We used the two-chamber reactor developed by Skrydstrup[234] where a solid CO precursor (COgen, **4.15**) is used to generate a controlled amount of carbon monoxide (Scheme **4.3**). Instead of a CO-containing product, we observed

an unexpected 79:21 mixture of the fluorene product **4.3a** together with the migratory SMC product 1,1-diarylalkane **4.4a**.



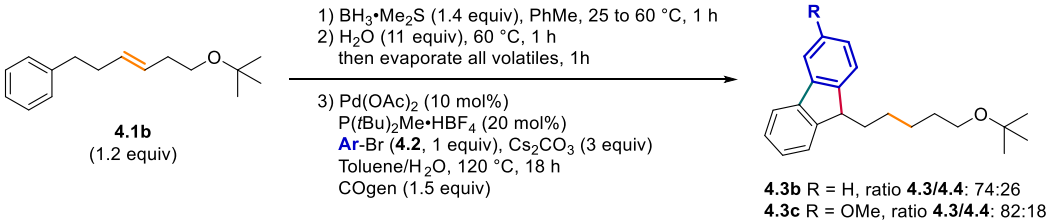
Scheme 4.3: Unexpected formation of 9-*n*-alkyl-fluorene product **4.3a**. Ratio of **4.3**/**4.4** determined by GCMS analysis.

Unknowing of the effect that carbon monoxide had on the reaction, we performed the same reaction but with a balloon of CO gas instead of the more expensive COgen two-chamber system (Scheme **4.4**). The fluorene product **4.3a** was again observed, but this time in a roughly one-to-one ratio with **4.4a**.



Scheme 4.4: Test-reaction with a CO balloon instead of COgen. Ratio of **4.3**/**4.4** determined by GCMS analysis.

Aiming at identifying a suitable model reaction for further optimisation we conducted the reaction with alkene **4.1b** and two different electrophiles in the two-chamber reactor as the ratio was higher in favour of the desired product **4.3** (Scheme **4.5**). The obtained ratios were comparable with the first reaction (Scheme **4.4**).

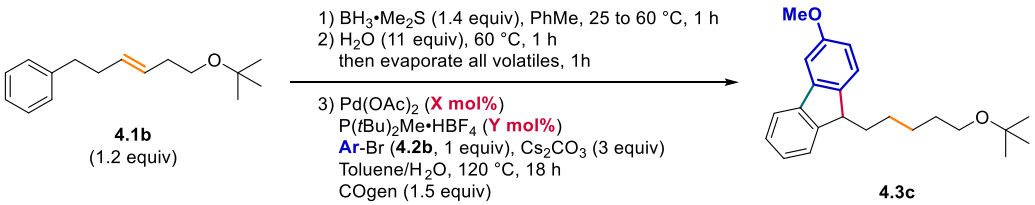


Scheme 4.5: Test-reactions with different electrophiles (**4.2a**, **4.2b**) on alkenyl arene **4.1b**. Ratio of **4.3**/**4.4** determined by GCMS analysis.

Still unknowing of the effect that CO had, we decided to check whether CO acts as a ligand. We therefore decided to test the reaction without the phosphine ligand, as well as with different catalyst loading to see if this affects the reactivity of the system (Table **4.1**). The reaction without ligand showed no reaction (entry **1**), indicating the necessity of a phosphine

ligand, at least for the migratory SMC. Decreasing to 5 mol% of the catalyst showed only minimal traces of the products (entry **2**). Surprisingly, we also observed only trace amounts of the products when the reaction was conducted under the same conditions as previously (entry **3**), indicating a lack of reproducibility.

Table 4.1: Different catalyst loading.



Entry	Amount of Pd	Amount of L	Ratio 4.3/4.4[a]
1	10 mol%	-	n.r.
2	5 mol%	10 mol%	traces
3	10 mol%	20 mol%	traces

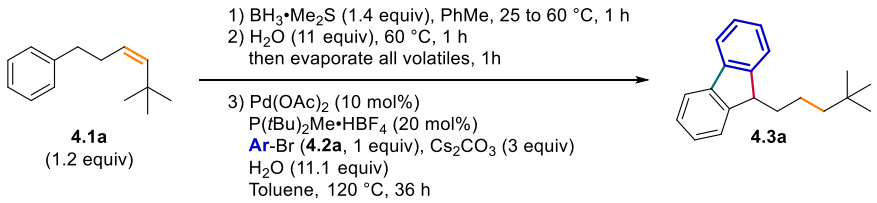
[a] Ratio of the cascade product (**4.3**) and migratory SMC product (**4.4**) determined by GC-MS analysis.

As we could not identify the role of the carbon monoxide, we decided to do a bottom-up optimisation without CO, starting from the same model-reaction as used for the optimisation of the migratory SMC (*see also* Section **3.2.2**)

4.2.2. Optimisation of the Reaction Conditions

As mentioned, we expect the carbonate necessary for the migratory SMC to be mainly in the aqueous phase. Thus, we started with the screening of different carboxylates, which have a higher solubility in the organic solvent due to an organic back-bone (Table **4.2**). The reaction with caesium pivalate, which is often employed in C-H activation reactions, furnished surprisingly only a very small amount of the product (entry **1**). Caesium acetate as well as *in situ* generated adamantly carboxylate gave a slightly better yield, but still less good than the one previously obtained.

Table 4.2: Screening of additives known to favour the CMD.

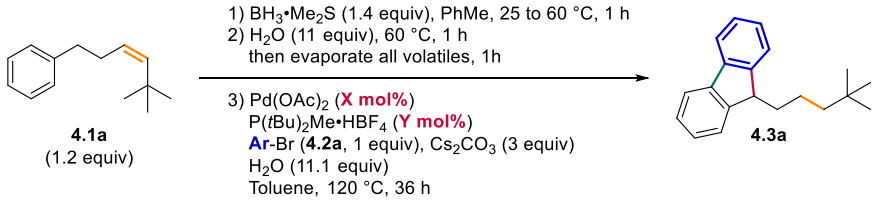


Entry	Additive	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	CsOPiv (30 mol%)	5	75
2	CsOAc (30 mol%)	16	70
3	$AdCO_2H$ (30 mol%)	24	56

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard.

As the palladium catalyst has a bigger workload for this cascade process, we then tested higher catalyst loading (Table **4.3**). The reaction with 10 mol% of the catalyst gave 61% of the product **4.4** (entry **1**) which was gratifying, but the yield decreased when more catalyst was added (entry **2**, **3**). So we decided to keep running the reaction with 10 mol% of catalyst.

Table 4.3: Screening of the catalyst loading.

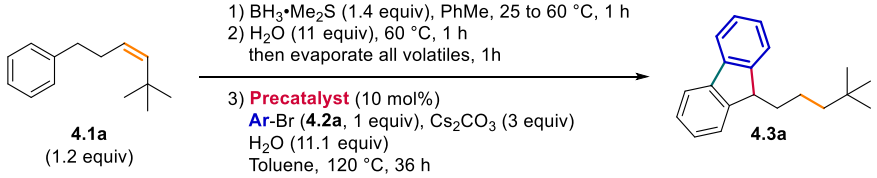


Entry	Amount of Pd	Amount of L	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	10 mol%	20 mol%	61	29
2	15 mol%	30 mol%	39	47
3	20 mol%	40 mol%	37	47

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard.

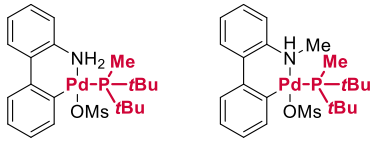
As the Pd^{II} is presumably reduced by one equivalent of the phosphine ligand, we decided to test the reaction with the precatalyst (**4.16**, **4.17**) developed by Buchwald[235,236] which generates *in situ* a Pd^0L catalyst together with 1-adamantanecarboxylic acid (Table **4.4**). The catalyst were reactive and showed nearly complete conversion of the initial boronic acid obtained from the alkene **4.1a**, but with unsatisfying ratios of the products (entry **1**, **2**).

Table 4.4: Screening of Buchwald's precatalyst with L = P(*t*Bu)$_2$Me.



Entry	Additive	Precat.	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	$AdCO_2H$ (30 mol%)	**4.16**	42	49
2	$AdCO_2H$ (30 mol%)	**4.17**	36	57

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard.



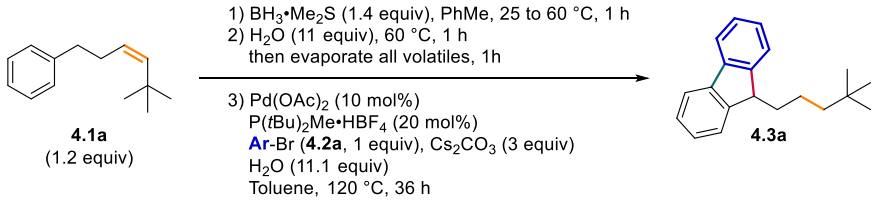
4.16 R = H,
(Pd-G3-P(*t*Bu)$_2$Me)

4.17 R = Me,
(Pd-G4-P(*t*Bu)$_2$Me)

As we could still not define the parameters that were detrimental for the reaction, we decided to do some test-reactions by arbitrarily variating some of the conditions (Table **4.5**). The reaction with P(*t*Bu)$_3$·HBF$_4$ (**L4.2**) as ligand showed hardly any conversion (entry **1**), whereas an interesting ratio was obtained with PCy_3·HBF$_4$ (**L4.3**, entry **2**). Raising the temperature to 140 °C gave a high yield and good ratio (entry **3**) as for the reaction with less water (entry **4**).

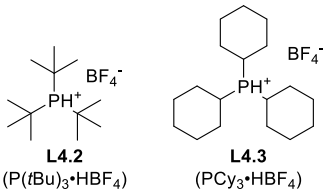
Surprisingly, we also observed the formation of 78% of the product **4.3a** with a very good ratio when the reaction was performed without water (entry **5**). However, when the reaction was repeated, we only observed some of the intermediate product **4.4a** and no **4.3a** at all (entry **5**, results in parenthesis), confirming the non-reproducibility of the reaction. Additionally, the reaction with caesium pivalate instead of caesium carbonate showed no conversion at all.

Table 4.5: Further screening of reaction conditions.



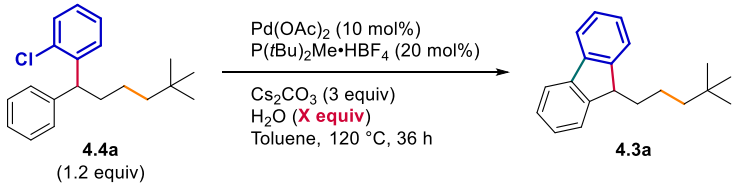
Entry	Variation from std. conditions	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	ligand: $P(tBu)_3 \cdot HBF_4$	0	7
2	ligand: $PCy_3 \cdot HBF_4$	54	24
3	temperature: 140 °C	77	3
4	H_2O: 5.5 equiv	77	11
5	without H_2O	78 *(0)*[b]	8 *(53)*[b]
6	base: CsOPiv	-	-
7	base: CsOPiv; without H_2O	-	-

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard; [b] Yield in parenthesis obtained when the reaction was performed a second time.



It seemed from the obtained results, that the presence of water is detrimental for the second step to occur. This could also explain why the results are not reproducible, as the small amount of water in the catalysis tube can partially evaporate over the long reaction time. To confirm this, we engaged in the final step of our sequence the isolated intermediate **4.4a** with and without water (Table **4.6**). The reaction yielded 94% of the product in the absence of water (entry **1**), whereas only 1.2 equivalents of water were enough to drop the yield to 61% (entry **2**).

Table 4.6: C(sp^2)-H activation starting from the 1,1-diarylakane **4.4a**.

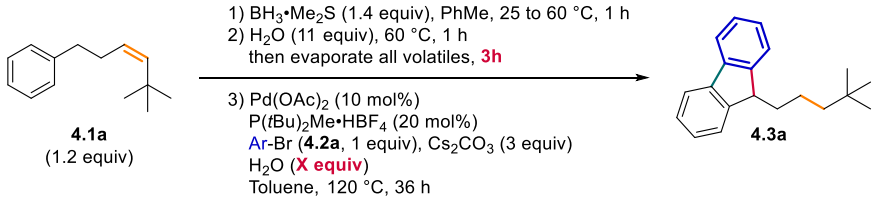


Entry	Amount of H_2O	Yield 4.3a (%)[a]
1	0 equiv	94
2	1.2 equiv	61

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard

This confirmed our supposition that water inhibits the second cycle of the cascade process. However, a certain amount of water is necessary for the migratory SMC to occur. In order to identify the precise amount necessary, which after consumption would not disturb the C-H activation, we prolonged the evaporation time succeeding the hydroboration and screened different amounts of water. (Table **4.7**). The reaction with 1.1 equivalents of water furnished 74% of the migratory SMC product **4.4a**, but no fluorene product **4.3a** at all (entry **1**), which was surprising as the water would have been nearly completely consumed at this stage. Doubling the amount of water yielded 49% of the product **4.3a**, but a consequential 37% amount of intermediate **4.4a** also remained (entry **2**). Further increasing the amount of water lead to better results in terms of yield and ratio (entry **3**, **4**), thus refuting our assumption.

Table 4.7: Screening of the amount of water after prolonged evaporation time.

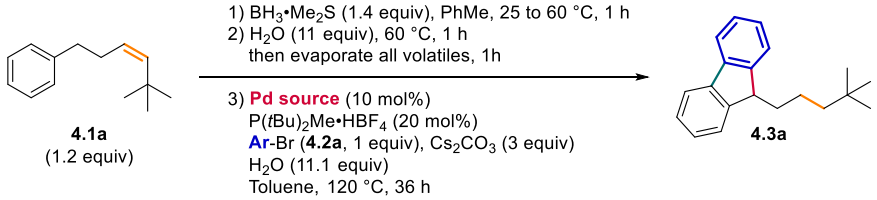


Entry	Amount of H_2O	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	1.1 equiv	0	74
2	2.2 equiv	49	37
3	5.6 equiv	72	13
4	11.1 equiv	75	4

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard

We then continued by comparing palladium acetate with palladium pivalate (Table **4.8**). However, the reaction with $Pd(OAc)_2$ only furnished 22% of the product **4.3a** with a lot of the intermediate remaining (entry **1**). $Pd(OPiv)_2$ gave a better yield and ratio (entry **2**), although better results were previously obtained.

Table 4.8: Testing a different palladium source.

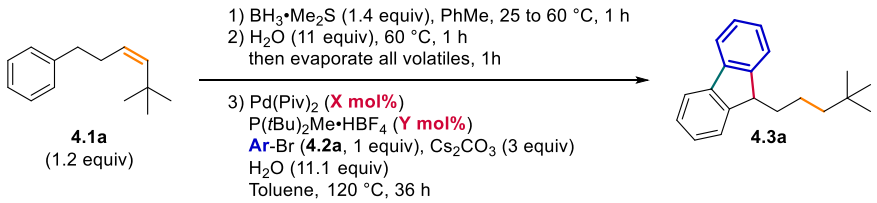


Entry	Pd source	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	$Pd(OAc)_2$	22	43
2	$Pd(OPiv)_2$	38	18

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard

As the ratio between the palladium and ligand had a big impact on the outcome of the migratory SMC (*see also* Table **2.15**) we wanted to check if this could favour the formation of the fluorene product **4.4** (Table **4.9**). A slight increase of the catalyst loading showed better reactivity (entry **1**), but reducing the amount of ligand was detrimental (entry **2**, **3**).

Table 4.9: Screening of the catalyst loading and Pd/L ratio.

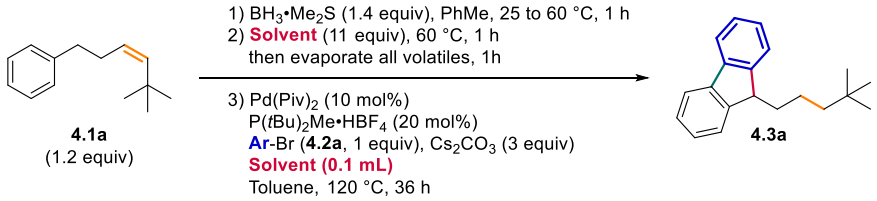


Entry	Amount of Pd	Amount of L	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	15 mol%	30 mol%	56	10
2	10 mol%	15 mol%	36	34
3	10 mol%	10 mol%	21	56

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard.

In the last attempt, we decided to check if the whole reaction could be performed in a protic solvent (Table **4.10**). However, no conversion was observed when methanol or isopropanol were used (entry **1**, **2**).

Table 4.10: Screening of different protic solvents.



Entry	Solvent	Yield 4.3a (%)[a]	Yield 4.4a (%)[a]
1	MeOH	-	-
2	*i*PrOH	-	-

[a] Yield determined by ^{1}H-NMR using CH_2Br_2 as the internal standard.

As the reaction was not reproducible, giving different results at every attempt, we decided to discontinue this project.

4.3. Conclusion

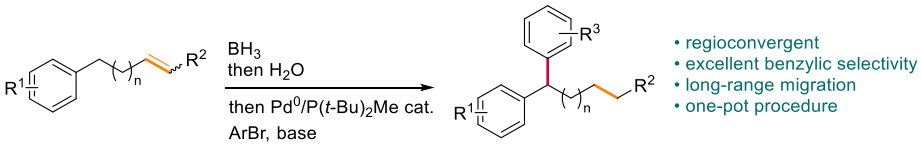
In summary, the goal of developing a cascade reaction consisting of a migratory SMC and a C(sp^2)-H activation was unsuccessful despite promising early results. Considerable efforts were made through screening of reaction conditions and analysis of the different reaction parameters, but the results were not reproducible. Possible reasons could be the prolonged reaction time, which can be challenging for palladium-phosphine catalysts, as well as conflicting presence of water. Thus we decided to discontinue this project, as the fluorene products can be readily obtained in an additional step from 1,1-diarylalkanes.

5. General Conclusion & Outlook

An impressive range of reactions have been accomplished for the migratory transition-metal catalysed remote C(sp^3)-functionalisation just over the last decade. This new approach constitutes an interesting and powerful extension to the organic synthesis toolbox, providing access to molecular complexity in a step- and atom-economical manner. On this basis, the present PhD thesis was directed towards the identification and development of novel transition-metal catalysed migratory functionalisation, with emphasis on the Suzuki-Miyaura cross-coupling.

The initial goal to develop the terminal-selective remote functionalisation of linear alkenes through a migratory Suzuki-Miyaura cross-coupling was encountered with unsatisfactory yields despite excellent regioselectivity. However, we observed a considerable preference for the developed palladium-catalyst to undergo reductive elimination at a benzylic site when different substrates were tested. Thus, we decided to exploit this behaviour in the optimisation of a novel project.

Therefore, we proceeded with the development of the benzylic-selective remote functionalisation through a migratory Suzuki-Miyaura cross-coupling (Scheme **5.1**). Linear alkenyl arenes were successfully converted to 1,1-diarylalkanes in up to quantitative yields, and in most cases with perfect regioselectivity. The designed one-pot procedure avoids the difficult purification and isolation of the *sec*-alkylboronic acid intermediates. We also demonstrated the regioconvergent nature of this type of reaction as well as the long-range migration up to ten positions, and mechanistic experiments indicated a partially reversible, non-dissociative palladium migration along the alkyl chain until the benzylic position is reached, where reductive elimination is favoured.



Scheme 5.1: One-Pot Alkene Hydroboration/Palladium-Catalysed Migratory Suzuki-Miyaura Cross-Coupling.

Further efforts of extending the reaction to a cascade process involving a C(sp^2)-H activation for the preparation of 9-*n*-alkyl fluorenes were in vain, as the role of the required water for the migratory Suzuki-Miyaura cross-coupling was unclear for the C-H activation.

The field of migratory cross-coupling is rapidly and continuously growing due to the synthetic potential, and a multitude of approaches were already disclosed. Elegant examples of enantioselective Heck-type reactions as well as stereospecific transformations were already reported. However, asymmetric examples remain scarce, especially for enantioselective terminating steps, although its feasibility was disclosed in the initial report of the Baudoin group in 2010. We therefore expect a great expansion in this field of migration in the future research.

6. Experimental Section

6.1. General Information

6.1.1. Techniques

All reactions involving air-sensitive materials were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glovebox. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains ($KMnO_4$ and Phosphomolybdic acid). Flash column chromatography (FCC) was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system.

6.1.2. Chemicals

Anhydrous solvents were obtained from a solvent purification system equipped with activated alumina and copper columns. The solvents were degassed by three cycles of freeze-pump-thaw and storing in single-necked flasks equipped with a J-Young PTFE valve (or similar) when necessary. Chemical reagents were purchased from Merck (Sigma-Aldrich), Acros Organics, AlfaAesar Apollo scientific and Fluorochem and used as received without further purification unless otherwise stated.

6.1.3. Instrumentation:

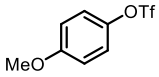
GC-MS analyses were performed with a Shimadzu QP2010SB GCMS apparatus on a Rtx®-5ms-Low-Bleed column lined with a mass (EI) detection system. Melting points were obtained on a Büchi melting point M-565, and are uncorrected. IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimetres (cm^{-1}). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 400 (400 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm) unless otherwise noted. ^{19}F NMR spectra were referenced to external $CFCl_3$, ^{11}B NMR spectra were referenced to external $BF_3{\cdot}Et_2O$ and ^{31}P NMR spectra were referenced to external H_3PO_4. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and bs = broad singlet), coupling constant in Hz and integration. High resolution mass spectra were recorded by Dr. M. Pfeffer (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer with addition of $AgNO_3$ [1 mM] in difficult cases. Microwave reactions were performed with a Biotage® Initiator+ System.

6.2. Terminal Selective Migratory SMC

6.2.1. Synthesis of electrophiles

All electrophiles tested were either purchased from a commercial supplier, or were already available in the group library and described in previous thesis, except for the following electrophiles.

4-Methoxyphenyl trifluoromethanesulfonate (**2.21a**)



4-Methoxyphenol (5.38 g, 43.3 mmol, 1.0 equiv) was dissolved in pyridine (21 mL) and cooled to 0 °C. Trifluoromethanesulfonic anhydride (8.0 mL, 47.6 mmol, 1.1 equiv) was added dropwise to the reaction mixture, and then stirred at 25 °C for 14 h. Et_2O (50 mL) was added, the organic layer was washed with 1 M aq. HCl (3x 30 mL), dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (20% DCM in pentane) to obtain 4-methoxyphenyl trifluoromethanesulfonate (11.0 g, 43.0 mmol, 99%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[237]

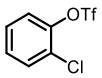
Rf = 0.3 (20% DCM in pentane)

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.23 – 7.17 (m, 2H), 6.95 – 6.89 (m, 2H), 3.82 (s, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 159.3, 143.2, 122.5, 118.9 (q, *J* = 320.9 Hz), 115.2, 55.8.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) -72.83

2-Chlorophenyl trifluoromethanesulfonate (**2.21h**)



2-Chlorophenol (2.48 g, 19.3 mmol, 1.0 equiv) was dissolved in pyridine (9.3 mL) and cooled to 0 °C. Trifluoromethanesulfonic anhydride (3.6 mL, 21.2 mmol, 1.1 equiv) was added dropwise to the reaction mixture, and then stirred at 25 °C for 14 h. Et_2O (30 mL) was added, the organic layer was washed with 1 M aq. HCl (3x 20 mL), dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (15% DCM in pentane) to obtain 2-Chlorophenyl trifluoromethanesulfonate (4.80 g, 18.4 mmol, 95%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[238]

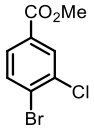
Rf = 0.4 (15% DCM in pentane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 – 7.49 (m, 1H), 7.41 – 7.30 (m, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 145.9, 131.5, 129.4, 128.5, 127.5, 123.2 (q, *J* = 1.0 Hz), 118. (q, *J* = 320.5 Hz).

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) -73.45

Methyl 4-bromo-3-chlorobenzoate (**2.2i**)



A drop of conc. sulfuric acid was added to a solution of 4-bromo-3-chlorobenzoic acid (4.99 g, 21.2 mmol, 1.0 equiv) in MeOH (20 mL, 494 mmol, 23.3 equiv) and the reaction mixture was stirred at 50 °C for 1 h. The volatiles were removed under reduced pressure and methyl 4-bromo-3-chlorobenzoate (4.74 g, 19.0 mmol, 90%) was obtained as an off-white solid. Spectroscopic data are consistent with those previously reported.[239]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H).

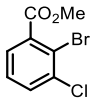
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 165.5, 135.1, 134.0, 131.4, 130.8, 128.8, 128.2, 52.7.

IR (neat): ν (cm^{-1}) 2953.0, 1728.5, 1588.6, 1435.0, 1376.7, 1287.8, 1240.0, 1104.7, 1021.7, 757.7.

MP: 62.7 °C.

HRMS (ESI): Calcd for $C_8H_6BrClO_2Na$ $[M+Na]^+$: 270.9132, found 270.9128

Methyl 2-bromo-3-chlorobenzoate (**2.2l**)



A drop of conc. sulfuric acid was added to a solution of 2-bromo-3-chlorobenzoic acid (500 mg, 2.12 mmol, 1.0 equiv) in MeOH (2 mL, 49.4 mmol, 23.3 equiv) and the reaction mixture was stirred at 50 °C for 1 h. The volatiles were removed under reduced pressure and methyl 2-bromo-3-chlorobenzoate (455 mg, 1.82 mmol, 86%) was obtained as colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 – 7.53 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 1H), 3.94 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 166.8, 136.7, 135.8, 132.8, 128.6, 128.1, 121.5, 53.0.

IR (neat): ν (cm^{-1}) 2952.3, 1732.6, 1431.9, 1283.2, 1199.5, 1136.8, 1032.8, 967.0, 756.8.

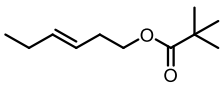
HRMS (ESI): Calcd for $C_8H_6BrClO_2Na$ $[M+Na]^+$: 270.9132, found 270.9131

6.2.2. Synthesis of alkenes

General procedure **A**: Wittig reaction

The triphenylphosphonium-bromide salt (1.0 equiv) was suspended in THF (2.4 mL/mmol) under inert conditions. *n*-BuLi (1.6 M in hexanes, 1.1 equiv) was added dropwise at 0 °C and the reaction mixture was left to stir at 0 °C for 1 h. The aldehyde (1.0 equiv) was then added dropwise to the reaction mixture. After removal of the cooling bath and stirring for 14 h under reflux the reaction mixture was slowly quenched with water, extracted with cyclohexane, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FCC.

(*E*)-hex-3-en-1-yl pivalate (**2.1c**)



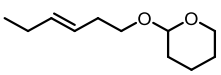
(*E*)-3-Hexen-1-ol (0.5 mL, 4.08 mmol, 1.0 equiv) and DMAP (49.8 mg, 0.408 mmol, 0.1 equiv) were dissolved in DMC (8.0 mL). Et_3N (1.1 mL, 8.16 mml, 2.0 equiv) and pivaloyl chloride (0.6 mL, 4.90 mmol, 1.2 equiv) where then added and the reaction mixture was stirred for 15 h at 25 °C before water (10 mL) was added. The aqueous phases was extracted with DCM (3x 20 mL) and the combined organic layers dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude product purified by FCC (5% EtOAc in Cy) to obtain (*E*)-hex-3-en-1-yl pivalate (527 mg, 2.86 mmol, 70%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[240]

Rf = 0.3 (5% EtOAc in Cy)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 5.61 – 5.47 (m, 1H), 5.44 – 5.29 (m, 1H), 4.06 (t, *J* = 6.7 Hz, 2H), 2.36 – 2.25 (m, 2H), 2.07 – 1.95 (m, 2H), 1.18 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 178.7, 135.1, 124.4, 64.0, 38.9, 32.2, 27.3, 25.8, 13.9.

(*E*)-2-(hex-3-en-1-yloxy)tetrahydro-2H-pyran (**2.1d**)



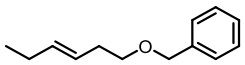
3,4-Dihydro-(2H)-pyran (1.1 mL, 12.2 mmol, 3.0 equiv) was added to a solution of (*E*)-3-Hexen-1-ol (0.5 mL, 4.08 mmol, 1.0 equiv) in DCM (10 mL). Then, a catalytic amount of *p*-toluenesulfonic-acid was added and the reaction mixture stirred for 1.5 h at 25 °C. The reaction mixture was diluted with DCM (30 mL) and washed with sat. aq. Na_2CO_3 (25 mL), brine (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (5% Et_2O in cyclohexane) to obtain (*E*)-2-(hex-3-en-1-yloxy)tetrahydro-2H-pyran (465 mg, 2.52 mmol, 62%) as a colourless liquid. Spectroscopic data are consistent with those previously reported.[241]

Rf = 0.34 (5% Et_2O in Cy)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 5.60 – 5.47 (m, 1H), 5.47 – 5.35 (m, 1H), 4.59 (s, 1H), 3.87 (s, 1H), 3.77 – 3.69 (m, 1H), 3.53 – 3.45 (m, 1H), 3.45 – 3.37 (m, 1H), 2.33 – 2.24 (m, 2H), 2.05 – 1.95 (m, 2H), 1.88 – 1.76 (m, 1H), 1.75 – 1.65 (m, 1H), 1.64 – 1.45 (m, 4H), 0.96 (t, J = 7.5 Hz, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 134.3, 125.3, 98.9, 67.5, 62.4, 33.2, 30.9, 25.8, 25.6, 19.8, 14.0.

(*E*)-((hex-3-en-1-yloxy)methyl)benzene (**2.1e**)



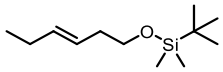
Sodium hydride (60% in mineral oil, 196 mg, 4.90 mmol, 1.2 equiv) was added portionwise to a solution of (*E*)-3-Hexen-1-ol (0.5 mL, 4.08 mmol, 1.0 equiv) in THF (9.0 mL) at 0 °C and stirred for 15 min. TBAI (15.1 mg, 0.049 mmol, 0.01 equiv) and benzyl bromide (0.54 mL, 4.49 mmol, 1.1 equiv) were added, and the reaction mixture stirred for 4 h at 25 °C. The reaction was quenched with water (5.0 mL), extracted with Et_2O (3x 25 mL) and the combined organic layers were dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude product purified by FCC (5% Et_2O in cyclohexane) to obtain (*E*)-((hex-3-en-1-yloxy)methyl)benzene (722 mg, 3.79 mmol, 93%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[242]

Rf = 0.31 (5% Et_2O in Cy)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.31 (m, 4H), 7.33 – 7.24 (m, 1H), 5.63 – 5.50 (m, 1H), 5.50 – 5.34 (m, 1H), 4.52 (s, 2H), 3.54 – 3.45 (m, 2H), 2.38 – 2.26 (m, 2H), 2.09 – 1.96 (m, 2H), 1.02 – 0.93 (m, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 138.7, 134.3, 128.5, 127.8, 127.6, 125.3, 73.0, 70.4, 33.2, 25.8, 13.9.

(*E*)-*tert*-butyl(hex-3-en-1-yloxy)dimethylsilane (**2.1f**)



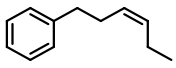
tert-Butyldimethylsilyl chloride (0.9 mL, 5.30 mmol, 1.3 equiv) was added to a solution of (*E*)-3-Hexen-1-ol (0.5 mL, 4.08 mmol, 1.0 equiv) and imidazole (0.7 mL, 10.2 mmol, 2.5 equiv) in DMF (2.1 mL) and the reaction mixture was stirred for 18 h at 25 °C. The reaction mixture was diluted with cyclohexane (20 mL) and the organic layer washed with half-saturated brine (5x 20 mL) and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude product purified by FCC (5% Et_2O in cyclohexane) to obtain (*E*)-*tert*-butyl(hex-3-en-1-yloxy)dimethylsilane (809 mg, 3.77 mmol, 93%). Spectroscopic data are consistent with those previously reported.[243]

Rf = 0.3 (2.5% Et_2O in Cy)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 5.57 – 5.45 (m, 1H), 5.45 – 5.32 (m, 1H), 3.61 (t, *J* = 6.9 Hz, 2H), 2.26 – 2.15 (m, 2H), 2.07 – 1.94 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 134.3, 125.5, 63.6, 36.4, 26.1, 25.8, 18.5, 14.0, -5.1.

(*Z*)-Hex-3-en-1-ylbenzene (**2.1h**)



The title compound was obtained following general procedure **A** from propyltriphenylphosphonium bromide (6.47 g, 16.0 mmol, 1.0 equiv) and hydrocinnamaldehyde (2.4 mL, 18.1 mmol. 1.1 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-hex-3-en-1-ylbenzene (1.17 g, 7.29 mmol, 46%, *E*/Z = 21:79)as a colourless oil. Spectroscopic data are consistent with those previously reported.[244]

Rf = 0.8 (cyclohexane).

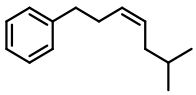
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 5.44 – 5.36 (m, 2H), 2.74 – 2.63 (m, 2H), 2.42 – 2.30 (m, 2H), 2.07 – 1.97 (m, 2H), 0.98 (*E-min*, t, *J* = 7.4 Hz), 0.92 (*Z-maj*, t, *J* = 7.5 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.4 (*E-min*), 142.3 (*Z-maj*), 132.8 (*E-min*), 132.5 (*Z-maj*), 128.6 (*E-min*), 128.6 (*Z-maj*), 128.5 (*E-min*), 128.4 (*Z-maj*), 128.4 (*E-min*), 128.2 (*Z-maj*), 125.9 (*Z-maj*), 125.8 (*E-min*), 36.3 (*E-min*), 36.2 (*Z-maj*), 34.61 (*E-min*), 29.2 (*Z-maj*), 25.7 (*E-min*), 20.7 (*Z-maj*), 14.4 (*Z-maj*), 14.1 (*E-min*).

IR (neat): ν (cm^{-1}) 3027.1, 2962.8, 1604.0, 1453.8, 1304.7, 1072.2, 967.6, 905.3.

HRMS (ESI): Calcd for $C_{12}H_{16}Ag$ $[M+Ag]^+$: 267.0297, found 267.0294.

(*Z*)-(6-Methylhept-3-en-1-yl)benzene (**2.1i**)



The title compound was obtained following general procedure **A** from isopentyltriphenylphosphoniumbromid (4.02 g, 9.25 mmol, 1.0 equiv) and hydrocinnamaldehyde (1.4 mL, 10.5 mmol. 1.1 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-(6-methylhept-3-en-1-yl)benzene (1.31 g, 6.98 mmol, 75%, *E/*Z = 20:80) as a colourless oil.

Rf = 0.78 (cyclohexane).

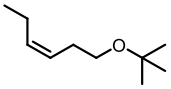
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 5.53 – 5.38 (m, 2H), 2.73 – 2.64 (m, 2H), 2.42 – 2.30 (m, 2H), 1.95 – 1.85 (m, 2H), 1.59 (dhept, *J* = 7.0, 6.5 Hz, 1H), 0.89 (*Z-maj*, d, *J* = 7.0 Hz, 6H) 0.87 (*E-min*, d, *J* = 7.0 Hz).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.3, 130.6 (*E-min*), 130.0 (*E-min*), 129.5 (*Z-maj*), 129.5 (*Z-maj*), 128.6 (*E-min*), 128.6 (*Z-maj*), 128.4 (*Z-maj*), 128.4 (*E-min*), 125.9 (*Z-maj*), 125.8 (*E-min*), 42.1 (*E-min*), 36.5 (*Z-maj*), 36.3 (*E-min*), 36.2 (*Z-maj*), 34.6 (*E-min*), 29.4 (*Z-maj*), 28.8 (*Z-maj*), 28.6 (*E-min*), 22.5 (*Z-maj*), 22.4 (*E-min*).

IR (neat): ν (cm^{-1}) 3027.1, 2954.7, 1604.2, 1454.8, 1383.3, 1076.3, 1030.6, 969.4, 827.2.

HRMS (ESI): Calcd for $C_{14}H_{20}Ag$ $[M+Ag]^+$: 295.0610, found 295.0609.

(*Z*)-1-(*tert*-Butoxy)hex-3-ene (**2.1j**)



Prepared according to an adapted reported procedure.[245] Anhydrous magnesium perchlorate (121 mg, 0.50 mmol, 0.1 equiv) was first dried *in vacuo* while heating using a heat gun and then was dissolved with (*Z*)-3-hexenol (0.6 mL, 5.00 mmol, 1.0 equiv) in dichloromethane (7.5 mL). Di-*tert*-butyl dicarbonate (2.6 mL, 11.5 mmol, 2.3 equiv) was added and the reaction

mixture was then stirred under reflux for 14 h. The mixture was first allowed to cool to 25 °C and water (25 mL) was added. The aqueous phase was extracted with DCM (3 x 25 mL) and then the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by FCC (2.5% Et_2O in PET) to (*Z*)-1-(*tert*-Butoxy)hex-3-ene (689 mg, 4.41 mmol, 88%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[246]

Rf = 0.41 (2.5% Et_2O in PET).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 5.47 – 5.41 (m, 1H), 5.37 – 5.29 (m, 1H), 3.32 (t, *J* = 7.3 Hz, 2H), 2.29 – 2.22 (m, 2H), 2.10 – 2.00 (m, 2H), 1.18 (s, 9H), 0.95 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 133.5, 125.3, 72.7, 61.6, 29.0, 28.0, 20.7, 14.4.

6.2.3. Synthesis of ligands

All ligands tested were either purchased from a commercial supplier, or were already available in the group library and described in previous thesis, except for the following phosphine ligands.

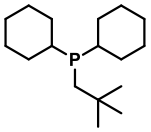
General procedure **B**: Grignard reaction with dialkylchlorophosphine

The whole procedure was carried out under inert atmosphere due to the pyrophoric nature of the starting material as well as product. The Grignard reagent (1.1 equiv) was added dropwise to a solution of PR_2Cl (1 equiv) in Et_2O [0.2 M] at -78 °C. The reaction mixture was stirred overnight allowing to warm to 25 °C. The resulting suspension was filtered through a Schlenk-frit and the volatiles were removed under reduced pressure. The crude product was purified by distillation at $5*10^{-1}$ mbar using a heat gun to gradually increase the temperature to obtain the trialkylphosphine.

General procedure **C**: Preparation of the tetrafluoroborate salts of trialkylphosphines

Performed according to a literature procedure.[205] HBF_4 (48 wt% aqueous solution, 8 equiv) was added to a solution of trialkylphosphine (1 equiv) in DCM [0.1 M] and the resulting mixture was stirred vigorously for 5 min. The organic layer was then separated, dried over $MgSO_4$ and the volatiles removed under reduced pressure, providing the tetrafluoroborate salt of the phosphine.

Dicyclohexyl(neopentyl)phosphine (**L2.36**)



Neopentyl bromide (0.5 mL, 3.38 mmol, 0.25 equiv) was added to a suspension of magnesium turnings (361 mg, 14.9 mmol, 1.1 equiv) and a crystal of iodine in Et_2O (7.0 mL), and the reaction mixture was carefully heated to 40 °C until the exothermic reaction initiated. Neopentyl bromide (1.5 mL, 10.1 mmol, 0.75 equiv) was then added dropwise to the reaction mixture, which was stirred under reflux for 14 h. The obtained Grignard reagent was then used in the next step.

The title compound was obtained following general procedure **B** from chlorodicyclohexylphosphine (1.00 g, 4.30 mmol, 1.0 equiv) and neopentylmagnesium bromide (1.47 M, 3.2 mL, 4.73 mmol, 1.1 equiv) to obtain dicyclohexyl(neopentyl)phosphine (498 mg, 1.86 mmol, 43%) as a colourless oil.

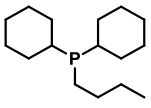
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.82 – 1.64 (m, 10H), 1.52 – 1.43 (m, 2H), 1.29 (d, *J* = 6.2 Hz, 2H), 1.27 – 1.08 (m, 10H), 0.95 (s, 9H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 36.2 (d, *J* = 19.8 Hz), 33.6 (d, *J* = 11.5 Hz), 31.1 (d, *J* = 8.6 Hz), 30.4 (d, *J* = 16.8 Hz), 30.3 (d, *J* = 13.4 Hz), 28.9 (d, *J* = 8.9 Hz), 27.6 (d, *J* = 10.9 Hz), 27.5 (d, *J* = 7.7 Hz), 26.8 (d, *J* = 1.1 Hz).

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) -14.93.

Butyldicyclohexylphosphine (**L2.37**)



The title compound was obtained following general procedure **B** from chlorodicyclohexylphosphine (1.00 g, 4.30 mmol, 1.0 equiv) and *n*-butylmagnesium chloride (2 M, 2.4 mL, 4.73 mmol, 1.1 equiv) to obtain butyldicyclohexylphosphine (802 mg, 3.14 mmol, 73%) as a colourless oil.

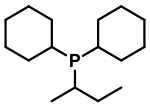
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.86 – 1.66 (m, 10H), 1.54 – 1.45 (m, 2H), 1.43 – 1.31 (m, 6H), 1.28 – 1.13 (m, 10H), 0.90 (t, *J* = 6.9 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 33.5 (d, *J* = 12.3 Hz), 30.9 (d, *J* = 18.5 Hz), 30.5 (d, *J* = 14.3 Hz), 29.2 (d, *J* = 7.9 Hz), 27.6 (d, *J* = 11.4 Hz), 27.5 (d, *J* = 7.8 Hz), 26.7 (d, *J* = 1.1 Hz), 24.8 (d, *J* = 12.1 Hz), 21.1 (d, *J* = 15.8 Hz), 14.0.

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) -4.15.

sec-Butyldicyclohexylphosphine (**L2.38**)



The title compound was obtained following general procedure **B** from chlorodicyclohexylphosphine (1.00 g, 4.30 mmol, 1.0 equiv) and *s*-butylmagnesium chloride (1.85 M, 2.6 mL, 4.73 mmol, 1.1 equiv) to obtain *sec*-butyldicyclohexylphosphine (302 mg, 27.4 mmol, 27%) as a colourless oil.

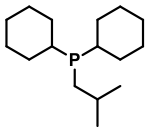
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) 1.85 – 1.47 (m, 14H), 1.36 – 1.14 (m, 11H), 1.08 (dd, *J* = 10.4, 7.0 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 32.3 (d, *J* = 33.4 Hz), 28.5 (d, *J* = 34.6 Hz), 27.4 (d, *J* = 3.9 Hz), 26.7 (d, *J* = 12.1 Hz), 25.4 (d, *J* = 4.4 Hz), 24.0 (d, *J* = 2.8 Hz), 13.7 (d, *J* = 3.4 Hz), 12.7 (d, *J* = 13.6 Hz).

^{31}P-NMR (101 MHz, $CDCl_3$): δ (ppm) 10.72.

Dicyclohexyl(isobutyl)phosphine (**L2.39**)



The title compound was obtained following general procedure **B** from chlorodicyclohexylphosphine (1.00 g, 4.30 mmol, 1.0 equiv) and *s*-butylmagnesium chloride (2 M, 2.4 mL, 4.73 mmol, 1.1 equiv) to obtain dicyclohexyl(isobutyl)phosphine (502 mg, 1.97 mmol, 46%) as a colourless oil.

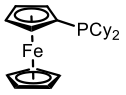
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.80 – 1.67 (m, 10H), 1.51 – 1.43 (m, 2H), 1.28 – 1.11 (m, 13H), 0.98 (d, *J* = 6.6 Hz, 6H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 33.6 (d, *J* = 11.8 Hz), 31.8 (d, *J* = 17.1 Hz), 30.4 (d, *J* = 14.3 Hz), 28.9 (d, *J* = 7.9 Hz), 28.1 (d, *J* = 18.4 Hz), 27.5 (d, *J* = 20.2 Hz), 24.3 (d, *J* = 9.3 Hz).

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) -9.56.

Dicyclohexylferrocenylphosphine (**L2.40**)



Ferrocene (407 mg, 2.18 mmol, 1.0 eq.) was dissolved in THF (1.5 mL) and hexane (1.5 mL). At 0 °C, *t*-BuLi (2.1 M, 2.1 mL, 4.36 mmol, 2.0 equiv) was slowly added and the solution was stirred for 30 minutes. Chlorodicyclohexylphosphine (507 mg, 2.18 mmol, 1.0 equiv) in Et_2O (5.0 mL) was added dropwise to the reaction mixture. The solution was stirred for 1.5 h at 0 °C followed by 1 hour at room temperature. Aqueous NaOH (1 M, 8.0 mL) and brine (8.0 mL) were added, the layers were separated and the aqueous layer was extracted with EtOAc (12 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (20% Et_2O in pnetane), and was then recrystallized 3 times from *n*-heptane to obtain dicyclohexylferrocenylphosphine (114 mg, 0.298 mmol, 14%) as a yellow solid

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 4.29 (m, 2H), 4.17 – 4.15 (m, 2H), 4.14 (s, 5H), 1.86 – 1.69 (m, 10H), 1.30 – 1.01 (m, 12H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 71.7 (d, *J* = 11.2 Hz), 69.3, 33.6 (d, *J* = 11.4 Hz), 30.4 (d, *J* = 7.0 Hz), 30.3, 27.6, 27.5 (d, *J* = 8.9 Hz), 26.6.

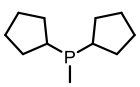
^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) -7.35.

IR (neat): ν (cm^{-1}) 3096.0, 2948.9, 2892.3, 1461.2, 1381.7, 1026.9, 818.3.

MP: 44.5 °C.

HRMS (ESI): Calcd for $C_{17}H_{26}FeP$ $[M\text{-}Cp]^+$: 317.1116 , found 317.1114.

Dicyclopentyl(methyl)phosphine (**L2.45**)



The title compound was obtained following general procedure **B** from chlorodicyclopentylphosphine (800 mg, 3.91 mmol, 1.0 equiv) and methylmagnesium bromide (2.9 M, 1.5 mL, 4.30 mmol, 1.1 equiv) to obtain dicyclopentyl(methyl)phosphine (300 mg, 1.63 mmol, 42%) as a colourless oil.

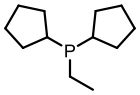
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.85 (m, 2H), 1.81 – 1.46 (m, 12H), 1.43 – 1.29 (m, 4H), 0.94 (d, *J* = 1.7 Hz, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 37.9 (d, *J* = 8.8 Hz), 30.9 (d, *J* = 17.7 Hz), 29.8 (d, *J* = 11.7 Hz), 26.7 (d, *J* = 7.4 Hz), 26.2 (d, *J* = 6.1 Hz).

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) -16.79.

Dicyclopentyl(ethyl)phosphine (**L2.46**)



The title compound was obtained following general procedure **B** from chlorodicyclopentylphosphine (800 mg, 3.91 mmol, 1.0 equiv) and ethylmagnesium bromide (0.86 M, 5.0 mL, 4.30 mmol, 1.1 equiv) to obtain dicyclopentyl(ethyl)phosphine (297 mg, 1.51 mmol, 39%) as a colourless oil.

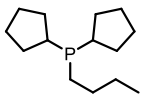
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.89 – 1.77 (m, 6H), 1.69 – 1.49 (m, 8H), 1.47 – 1.30 (m, 6H), 1.08 (dt, *J* = 12.5, 7.7 Hz, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 35.7 (d, *J* = 10.7 Hz), 31.2 (d, *J* = 16.9 Hz), 30.4 (d, *J* = 13.2 Hz), 26.6 (d, *J* = 7.4 Hz), 26.2 (d, *J* = 6.6 Hz), 17.3 (d, *J* = 13.4 Hz), 10.6 (d, *J* = 11.7 Hz).

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 0.29.

Butyldicyclopentylphosphine (**L2.47**)



The title compound was obtained following general procedure **B** from chlorodicyclopentylphosphine (800 mg, 3.91 mmol, 1.0 equiv) and *n*-butylmagnesium chloride (2 M, 2.2 mL, 4.30 mmol, 1.1 equiv) to obtain butyldicyclopentylphosphine (604 mg, 2.65 mmol, 68%) as a colourless oil.

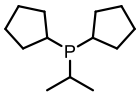
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) δ 1.87 – 1.75 (m, 6H), 1.68 – 1.59 (m, 4H), 1.59 – 1.48 (m, 4H), 1.46 – 1.28 (m, 10H), 0.89 (t, *J* = 7.1 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 36.2 (d, *J* = 10.5 Hz), 31.2 (d, *J* = 16.6 Hz), 30.4 (d, *J* = 12.7 Hz), 29.1 (d, *J* = 12.5 Hz), 26.6 (d, *J* = 7.3 Hz), 26.2 (d, *J* = 6.5 Hz), 24.9 (d, *J* = 10.1 Hz), 24.6 (d, *J* = 14.0 Hz), 14.0.

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) -4.23.

Dicyclopentyl(isopropyl)phosphine (**L2.48**)



The title compound was obtained following general procedure **B** from chlorodicyclopentylphosphine (800 mg, 3.91 mmol, 1.0 equiv) and *i*-propylmagnesium chloride (2 M, 2.2 mL, 4.30 mmol, 1.1 equiv) to obtain dicyclopentyl(isopropyl)phosphine (498 mg, 2.35 mmol, 60%) as a colourless oil.

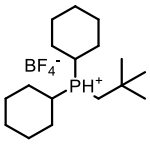
IR and HRMS were not measured as the product is not stable towards air.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1.88 – 1.80 (m, 6H), 1.67 – 1.59 (m, 4H), 1.59 – 1.26 (m, 9H), 1.12 (dd, *J* = 10.9, 7.2 Hz, 6H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 34.3 (d, *J* = 13.4 Hz), 31.9 (d, *J* = 16.6 Hz), 31.6 (d, *J* = 15.9 Hz), 26.4 (d, *J* = 7.3 Hz), 26.1 (d, *J* = 7.4 Hz), 24.3 (d, *J* = 13.2 Hz), 19.9 (d, *J* = 8.9 Hz).

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 14.95.

Dicyclohexyl(neopentyl)phosphine tetrafluoroborate (**L2.49**)



The title compound was obtained following general procedure **C** from dicyclohexyl(neopentyl)phosphine (**L2.36**, 100 mg, 0.373 mmol, 1.0 equiv) to obtain dicyclohexyl(neopentyl)phosphine tetrafluoroborate (132 mg, 0.370 mmol, 99%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.60 – 5.49 (m, 1H), 2.56 – 2.40 (m, 2H), 2.08 – 1.79 (m, 10H), 1.48 – 1.35 (m, 7H), 1.34 – 1.22 (m, 3H), 1.15 (s, 9H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 30.9 (d, *J* = 5.1 Hz), 30.6 (d, *J* = 6.7 Hz), 29.1 (d, *J* = 42.3 Hz), 27.5 (d, *J* = 3.6 Hz), 27.1 (d, *J* = 39.7 Hz), 26.7 (d, *J* = 3.7 Hz), 26.2 (d, *J* = 6.0 Hz), 26.1 (d, *J* = 5.8 Hz), 25.2 (d, *J* = 1.8 Hz).

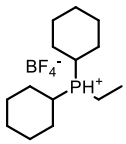
^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 13.07.

IR (neat): ν (cm^{-1}) 2936.3, 2859.6, 1451.5, 1053.7.

MP: 150.4 °C.

HRMS (ESI): Calcd for $C_{17}H_{34}P$ $[M\text{-}BF_4]^+$: 269.2393, found 269.2394.

Dicyclohexyl(ethyl)phosphine tetrafluoroborate (**L2.50**)



The title compound was obtained following general procedure **C** from dicyclohexyl(ethyl)phosphine (100 mg, 0.442 mmol, 1.0 equiv) to obtain dicyclohexyl(ethyl)phosphine tetrafluoroborate (139 mg, 0.442 mmol, quant.) as a white solid, with impurities araising from the commercial starting material. Spectroscopic data are consistent with those previously reported.[247]

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.32 (t, *J* = 4.8 Hz, 1H), 5.36 (t, *J* = 4.8 Hz, 1H), 2.04 – 1.81 (m, 12H), 1.47 – 1.22 (m, 15H).

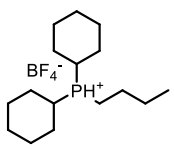
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 28.3 (d, *J* = 42.1 Hz), 27.7 (d, *J* = 3.5 Hz), 27.1 (d, *J* = 3.5 Hz), 26.3 – 25.94 (m), 25.2 (d, *J* = 1.6 Hz), 8.4 (d, *J* = 6.0 Hz), 7.7 (d, *J* = 44.4 Hz).

^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 27.64.

IR (neat): ν (cm^{-1}) 2933.2, 2858.1, 1451.4, 1280.0, 1055.0, 903.8, 766.1.

HRMS (ESI): Calcd for $C_{14}H_{28}P$ $[M\text{-}BF_4]^+$: 227.1923, found 227.1927.

Butyldicyclohexylphosphine tetrafluoroborate (**L2.51**)



The title compound was obtained following general procedure **C** from butyldicyclohexylphosphine (**L2.37**, 100 mg, 0.394 mmol, 1.0 equiv) to obtain butyldicyclohexylphosphine tetrafluoroborate (133 mg, 0.388 mmol, 99%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.53 – 5.21 (m, 1H), 2.55 – 2.45 (m, 2H), 2.19 (dd, *J* = 5.3, 3.3 Hz, 2H), 2.12 – 1.76 (m, 10H), 1.74 – 1.61 (m, 2H), 1.57 – 1.24 (m, 12H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 28.7, 28.4, 27.7 (d, *J* = 3.5 Hz), 27.1 (d, *J* = 3.5 Hz), 26.2 (d, *J* = 7.1 Hz), 26.1 (d, *J* = 13.0 Hz), 25.2 (d, *J* = 1.7 Hz), 24.2 (d, *J* = 14.5 Hz), 13.5 (d, *J* = 42.9 Hz), 13.5.

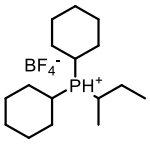
^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 24.53.

IR (neat): ν (cm^{-1}) 2931.5, 2863.1, 1453.5, 1051.1, 920.6, 868.3.

MP: 115.7 °C.

HRMS (ESI): Calcd for $C_{16}H_{32}P$ $[M\text{-}BF_4]^+$: 255.2236 , found 255.2241.

sec-Butyldicyclohexylphosphine tetrafluoroborate (**L2.52**)



The title compound was obtained following general procedure **C** from *sec*-butyldicyclohexylphosphine (**L2.38**, 100 mg, 0.394 mmol, 1.0 equiv) to obtain butyldicyclohexylphosphine tetrafluoroborate (130 mg, 0.380 mmol, 96%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.45 – 5.27 (m, 1H), 2.50 (dq, *J* = 10.4, 3.4 Hz, 3H), 2.11 – 1.74 (m, 12H), 1.65 – 1.52 (m, 5H), 1.47 – 1.32 (m, 8H), 1.12 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 28.5, 28.2, 28.1, 28.1, 28.1, 28.0, 28.0, 28.0, 27.8, 27.8, 26.5, 26.4, 26.4, 26.4, 26.4, 26.3, 26.3, 26.3, 25.4, 25.4, 25.4, 25.2, 25.2, 25.1, 14.3, 14.30, 12.3, 12.2. Doublets could not be assigned due to overlapping signals.

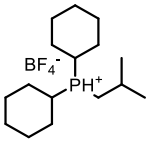
^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 29.98.

IR (neat): ν (cm^{-1}) 2936.7, 2861.4, 1453.4, 1051.2, 911.0, 728.7, 648.3.

MP: 151.4 °C.

HRMS (ESI): Calcd for $C_{16}H_{32}P$ $[M\text{-}BF_4]^+$: 255.2236 , found 255.2237.

Dicyclohexyl(isobutyl)phosphine tetrafluoroborate (**L2.53**)



The title compound was obtained following general procedure **C** from dicyclohexyl(isobutyl)phosphine (**L2.39**, 100 mg, 0.394 mmol, 1.0 equiv) to obtain dicyclohexyl(isobutyl)phosphine tetrafluoroborate (131 mg, 0.383 mmol, 97%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) δ 6.39 – 5.29 (m, 1H), 2.52 (dt, *J* = 11.9, 3.7 Hz, 2H), 2.13 – 1.95 (m, 7H), 1.94 – 1.84 (m, 4H), 1.83 – 1.74 (m, 2H), 1.54 – 1.36 (m, 8H), 1.29 (dd, *J* = 12.1, 3.6 Hz, 2H), 1.14 (dd, *J* = 6.2, 1.7 Hz, 6H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 28.9, 28.6, 27.6 (d, *J* = 3.6 Hz), 26.9 (d, *J* = 3.6 Hz), 26.1 (d, *J* = 28.6 Hz), 26.1 (d, *J* = 1.8 Hz), 25.6 (d, *J* = 5.1 Hz), 25.2 (d, *J* = 1.7 Hz), 22.5, 22.2.

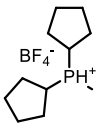
^{31}P-NMR (101 MHz, $CDCl_3$): δ (ppm) 19.29

IR (neat): ν (cm^{-1}) 2937.7, 2860.5, 1453.3, 1328.4, 1052.0, 912.7, 850.5, 777.2, 670.1.

MP: 143.8 °C.

HRMS (ESI): Calcd for $C_{16}H_{32}P$ $[M\text{-}BF_4]^+$: 255.2236 , found 255.2238.

Dicyclopentyl(methyl)phosphine tetrafluoroborate (**L2.54**)



The title compound was obtained following general procedure **C** from dicyclopentyl(methyl)phosphine (**L2.45**, 100 mg, 0.543 mmol, 1.0 equiv) to obtain dicyclopentyl(methyl)phosphine tetrafluoroborate (145 mg, 0.533 mmol, 98%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.90 – 5.25 (m, 1H), 2.77 – 2.59 (m, 2H), 2.28 – 2.05 (m, 4H), 1.92 – 1.57 (m, 15H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 28.9, 28.8, 28.5, 28.1 (d, *J* = 1.2 Hz), 26.3 (d, *J* = 10.9 Hz), 26.1 (d, *J* = 10.8 Hz), -0.35 (d, *J* = 50.9 Hz).

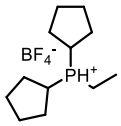
^{31}P-NMR (202 MHz, $CDCl_3$): δ (ppm) 21.96.

IR (neat): ν (cm^{-1}) 2957.9, 1051.9, 912.9, 730.7, 670.1.

MP: 127.9 °C.

HRMS (ESI): Calcd for $C_{11}H_{22}P$ $[M\text{-}BF_4]^+$: 185.1454, found 185.1456.

Dicyclopentyl(ethyl)phosphine tetrafluoroborate (**L2.55**)



The title compound was obtained following general procedure **C** from dicyclopentyl(ethyl)phosphine (**L2.46**, 100 mg, 0.504 mmol, 1.0 equiv) to obtain dicyclopentyl(ethyl)phosphin tetrafluoroborate (144 mg, 0.503 mmol, 99%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.68 – 5.28 (m, 1H), 2.75 – 2.63 (m, 2H), 2.34 (ddd, *J* = 12.8, 7.7, 4.8 Hz, 2H), 2.26 – 2.15 (m, 4H), 1.86 – 1.70 (m, 12H), 1.39 (dt, *J* = 19.2, 7.7 Hz, 3H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 29.1 (d, *J* = 1.4 Hz), 28.7 (d, *J* = 1.3 Hz), 28.1 (d, *J* = 46.7 Hz), 26.2 (d, *J* = 10.9 Hz), 26.0 (d, *J* = 10.9 Hz), 10.5 (d, *J* = 46.8 Hz), 7.8 (d, *J* = 5.6 Hz).

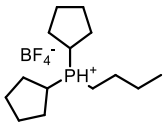
^{31}P-NMR (101 MHz, $CDCl_3$): δ (ppm) 29.96

IR (neat): ν (cm^{-1}) 2961.4, 1455.2, 1283.0, 1051.3, 913.3, 729.1.

MP: 171.1 °C.

HRMS (ESI): Calcd for $C_{12}H_{24}P$ $[M\text{-}BF_4]^+$: 199.1610, found 199.1614.

Butyldicyclopentylphosphine tetrafluoroborate (**L2.56**)



The title compound was obtained following general procedure **C** from butyldicyclopentylphosphine (**L2.47**, 100 mg, 0.442 mmol, 1.0 equiv) to obtain butyldicyclopentylphosphine tetrafluoroborate (135 mg, 0.430 mmol, 97%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.76 – 5.36 (m, 1H), 2.74 – 2.62 (m, 2H), 2.29 – 2.14 (m, 6H), 1.88 – 1.66 (m, 14H), 1.51 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 29.2 (d, *J* = 1.4 Hz), 28.7 (d, *J* = 1.3 Hz), 28.4 (d, *J* = 46.8 Hz), 26.2 (d, *J* = 11.1 Hz), 26.0 (d, *J* = 11.0 Hz), 25.6 (d, *J* = 5.0 Hz), 24.1 (d, *J* = 14.6 Hz), 16.3 (d, *J* = 45.4 Hz), 13.4.

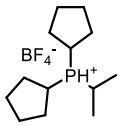
^{31}P-NMR (101 MHz, $CDCl_3$): δ (ppm)26.98.

IR (neat): ν (cm^{-1}) 2961.8, 2873.8, 2361.0, 1455.8, 1050.1, 915.0, 729.5.

MP: 174.9 °C.

HRMS (ESI): Calcd for $C_{14}H_{28}P$ $[M\text{-}BF_4]^+$: 227.1923, found 227.1925.

Dicyclopentyl(isopropyl)phosphine tetrafluoroborate (**L2.57**)



The title compound was obtained following general procedure **C** from dicyclopentyl(isopropyl)phosphine (**L2.48**, 100 mg, 0.471 mmol, 1.0 equiv) to obtain dicyclopentyl(isopropyl)phosphine tetrafluoroborate (141 mg, 0.0.470 mmol, 99%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.75 – 5.05 (m, 1H), 2.82 – 2.69 (m, 1H), 2.68 – 2.57 (m, 2H), 2.27 – 2.15 (m, 4H), 1.88 – 1.72 (m, 12H), 1.44 (dd, *J* = 17.9, 7.3 Hz, 6H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 29.5 (d, *J* = 1.5 Hz), 29.4 (d, *J* = 1.7 Hz), 27.5 (d, *J* = 44.1 Hz), 26.1 (d, *J* = 11.1 Hz), 25.8 (d, *J* = 11.1 Hz), 21.2 (d, *J* = 43.8 Hz), 17.5 (d, *J* = 2.5 Hz).

^{31}P-NMR (101 MHz, $CDCl_3$): δ (ppm) 35.80.

IR (neat): ν (cm^{-1}) 2965.2, 2875.1, 1464.0, 1268.8, 1050.7, 890.7, 729.9, 668.0.

MP: 211.1 °C.

HRMS (ESI): Calcd for $C_{13}H_{26}P$ $[M\text{-}BF_4]^+$: 213.1767, found 213.1770.

6.2.4. Palladium catalysed migratory arylation

General procedure **D**: Representative procedure for the screening of reaction conditions starting from trialkylboranes.

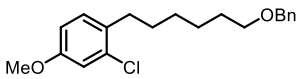
The reactions were performed on a 0.50 mmol scale. Unless otherwise noted: In a glovebox, an oven-dried 10 mL catalysis tube equipped with a stirring bar and septum was charged with the indicated palladium source, ligand, base and electrophile (if solid) as well as possible additives. Outside the glovebox, the solvent (1.0 mL), water (0.1 mL), aryl bromide (if liquid)

and the solution of trialkylborane (1 M in THF) were added. The septum was rapidly exchanged for a screw cap, the catalysis tube sealed with Teflon-tape, and then placed in a pre-heated heating block for 16 h. The reaction tube was then removed from the heating block and let to cool to 25 °C. The crude reaction mixture was then filtered over Celite® with EtOAc. Dodecane (1.0 equiv) was added to the crude, and an aliquot thereof was measured by GC-FID to determine the yield and ratio of the products.

General procedure **E**: One-pot hydroboration/migratory SMC

The reactions were performed on a 0.50 mmol scale. Unless otherwise noted: The olefin (0.600 mmol, 1.2 equiv) was charged in an oven-dried 10 mL catalysis tube equipped with a stirring bar and septum, and then purged and filled with Argon three times. A borane dimethyl sulfide complex solution in toluene (2 M, 0.35 mL, 0.700 mmol, 1.4 equiv) was then added and the tube placed in a metal heating block set at 50 °C with stirring, fitted with a balloon. After 1 h, the reaction tube was cooled to 0 °C with an ice-bath, water (0.10 mL, 5.55 mmol, 11.1 equiv) was added to the reaction mixture, and the reaction mixture was further stirred at 25 °C for 1 h. The balloon was then swapped with a line from the Schlenk and the volatiles were removed under high vacuum for 1 h. The tube was transferred in a glovebox and $Pd(OAc)_2$ (5.61 mg, 0.025 mmol, 5 mol%), $(t\text{Bu})_2\text{PMe}\bullet\text{HBF}_4$ (18.6 mg, 0.075 mmol, 15 mol%), Cs_2CO_3 (489 mg, 1.50 mmol, 3.0 equiv) and aryl bromide (0.500 mmol, 1.0 equiv) (if solid) were charged in the catalysis tube. Outside of the glovebox, xylenes (1.0 mL), water (0.1 mL) and the aryl bromide (0.500 mmol, 1.0 equiv) (if liquid) were added. The septum was rapidly exchanged for a screw cap, the catalysis tube sealed with Teflon-tape and then placed in a heating block set at 120 °C with vigorous stirring for 16 h. After this period the reaction mixture was allowed to cool to 25 °C and filtered over Celite® with EtOAc. The volatiles were removed under reduced pressure and the crude product was analyzed with GC-MS to determine the regioselectivity and then purified by FCC to yield the corresponding product.

1-(6-(Benzyloxy)hexyl)-2-chloro-4-methoxybenzene (**2.3i**)



The title compound was obtained following general procedure **E** from (*E*)-((hex-3-en-1-yloxy)methyl)benzene (**2.1d**, 114 mg, 0.600 mmol, 1.2 equiv) and 4-bromo-3-chloroanisole (79 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(benzyloxy)hexyl)-2-chloro-4-methoxybenzene (38.3 mg, 0.114 mmol, 23%) as a colourless oil.

Rf = 0.45 (2.5% EtOAc in Cy)

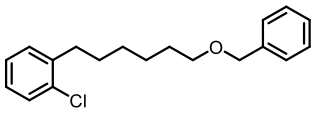
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.50 (s, 2H), 3.77 (s, 3H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 7.9 Hz, 2H), 1.67 – 1.54 (m, 4H), 1.43 – 1.27 (m, 4H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.4, 138.9, 134.3, 132.4, 130.8, 128.5, 127.8, 127.6, 114.5, 113.0, 73.0, 70.6, 55.6, 32.8, 30.1, 29.8, 29.3, 26.2.

IR (neat): ν (cm^{-1}) 2931.5, 2856.2, 1606.4, 1494.8, 1455.8, 1242.8, 1099.8, 1041.7, 840.5.

HRMS (ESI): Calcd for $C_{20}H_{25}ClO_2Na$ $[M+Na]^+$: 355.1435, found 355.1434.

1-(6-(Benzyloxy)hexyl)-2-chlorobenzene (**2.3h**)



The title compound was obtained following general procedure **E** from (*E*)-((hex-3-en-1-yloxy)methyl)benzene (**2.1d**, 114 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(Benzyloxy)hexyl)-2-chlorobenzene (48.1 mg, 0.159 mmol, 32%) as a colourless oil.

Rf = 0.41 (2.5% Et_2O in Cy)

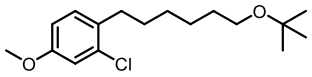
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 – 7.27 (m, 6H), 7.22 – 7.09 (m, 3H), 4.51 (s, 2H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.76 – 2.67 (m, 2H), 1.70 – 1.57 (m, 4H), 1.46 – 1.36 (m, 4H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 140.5, 138.9, 134.0, 130.5, 129.5, 128.5, 127.8, 127.6, 127.2, 126.8, 73.0, 70.6, 33.7, 29.8, 29.8, 30.0, 26.2.

IR (neat): ν (cm^{-1}) 2932.0, 2856.9, 1720.6, 1453.8, 1361.8, 1098.9, 906.9, 747.3, 696.7.

HRMS (ESI): Calcd for $C_{19}H_{23}ClONa$ $[M+Na]^+$: 325.1330, found 325.1325.

1-(6-(*tert*-Butoxy)hexyl)-2-chloro-4-methoxybenzene (**2.3i**)



The title compound was obtained following general procedure **E** from (*E*)-1-(*tert*-butoxy)hex-3-ene (**2.1j**, 93.8 mg, 0.600 mmol, 1.2 equiv) and 4-bromo-3-chloroanisole (79 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)hexyl)-2-chloro-4-methoxybenzene (32.4 mg, 0.108 mmol, 22%) as a colourless oil.

Rf = 0.42 (2.5% EtOAc in Cy)

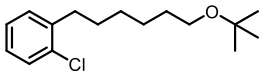
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 2.6 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.77 (s, 3H), 3.32 (t, *J* = 6.7 Hz, 2H), 2.69 – 2.61 (m, 2H), 1.59 – 1.51 (m, 4H), 1.42 – 1.36 (m, 4H), 1.18 (s, 9H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.3, 134.3, 132.5, 130.8, 114.8, 113.0, 72.6, 61.7, 55.6, 55.6, 32.8, 30.8, 30.1, 29.3, 26.2.

IR (neat): ν (cm^{-1}) 2932.8, 2361.6, 1606.6, 1495.4, 1462.2, 1361.6, 1237.8, 1197.4, 1082.0, 1042.6.

HRMS (ESI): Calcd for $C_{17}H_{27}ClO_2Na$ $[M+Na]^+$: 321.1592, found 321.1595.

1-(6-(*tert*-Butoxy)hexyl)-2-chlorobenzene (**2.3j**)



The title compound was obtained following general procedure **E** from (*E*)-1-(*tert*-butoxy)hex-3-ene (**2.1j**, 93.8 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-Butoxy)hexyl)-2-chlorobenzene (41.4 mg, 0.154 mmol, 31%) as a colourless oil.

Rf = 0.46 (2.5% Et_2O in Cy)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.17 (td, *J* = 7.3, 1.5 Hz, 1H), 7.14 – 7.08 (m, 1H), 3.32 (t, *J* = 6.7 Hz, 2H), 2.76 – 2.66 (m, 2H), 1.67 – 1.59 (m, 2H), 1.56 – 1.50 (m, 2H), 1.42 – 1.36 (m, 4H), 1.18 (s, 9H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 140.5, 134.1, 130.4, 129.5, 127.2, 126.8, 72.6, 61.7, 33.7, 30. 8, 29.9, 29.4, 27.7, 26.2.

IR (neat): ν (cm^{-1}) 2932.0, 2859.9, 1473.4, 1361.4, 1361.4, 1198.0, 1082.8, 876.5, 748.6.

HRMS (ESI): Calcd for $C_{16}H_{25}ClONa$ $[M+Na]^+$: 291.1486 , found 291.1484.

6.3. Benzylic Selective Migratory SMC

6.3.1. Synthesis of alkenes

General procedure **F**: Wittig reaction

The triphenylphosphonium-bromide salt (1.0 equiv) was suspended in THF (2.4 mL/mmol) under inert conditions. *n*-BuLi (1.6 M in hexanes, 1.1 equiv) was added dropwise at 0 °C and the reaction mixture was left to stir at 0 °C for 1 h. The aldehyde (1.0 equiv) was then added dropwise to the reaction mixture. After removal of the cooling bath and stirring for 14 h under reflux the reaction mixture was slowly quenched with water, extracted with cyclohexane, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FCC.

General procedure **G**: Sonogashira reaction of unactivated alkyl bromides

Performed according to a literature procedure.[248] 1,3-bis(l-adamantyl)imidazolium chloride or 1,3-bis(l-adamantyl)imidazolium tetrafluoroborate (5.0 mol%), CuI (7.5 mol%), [(n-allyl)PdCl]$_2$ (2.5 mol% and Cs_2CO_3 (1.4 equiv) were added in turn to a two-neck flask equipped with a stirring bar, a reflux condenser and a Schlenk-bubbler. The flask was then evacuated and backfilled with Argon three times. Then a mixture of Et_2O and DMF (2:1, 1.0 mL) was added, followed by the alkyne (1.3 equiv) and the alkyl halide (1.0 equiv). The heterogeneous reaction mixture was stirred vigorously at 45 °C for 14 h. The reaction mixture was allowed to cool down to 25 °C and was quenched with sat. aq. NH_4Cl. Et_2O was added and the organic phase was washed 5 times with half-saturated Brine The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was then purified by FCC or fractional distillation.

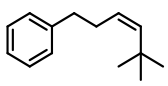
General procedure **H**: Nucleophilic substitution of alkyl bromides

Performed according to an adapted literature procedure.[249] *n*-BuLi (1.6 M in hexanes, 1.4 equiv) was added dropwise to a solution of the acetylene (1.3 equiv) in dry THF [1.0 M] at -78 °C under inert conditions and was stirred for 20 min at -78 °C. Then the alkylbromide (1.0 equiv) and HMPA (2.0 equiv) were added sequentially and the reaction mixture was allowed to warm to 25 °C while stirring for 4 h. The reaction mixture was then quenched with water, the layers seeparates and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified by FCC.

General procedure **I**: Partial hydrogenation of alkyne

Lindlar catalyst (10 mol% of Pd) was added to a solution of the alkyne (1.0 equiv) and quinoline (0.3 equiv) in cyclohexane [0.05 M]. Argon was bubbled through the solution for 5 minutes, followed by two balloons of hydrogen gas. The reaction mixture was then allowed to stir under a hydrogen atmosphere for 10 minutes. The reaction mixture was filtered over Celite®, concentrated *in vacuo* and the crude product purified by FCC.

(*Z*)-(5,5-Dimethylhex-3-en-1-yl)benzene (**3.1a**)



The title compound was obtained following general procedure **F** from (3-phenylpropyl)-triphenylphosphonium bromide (10.6 g, 23.0 mmol, 1.0 equiv) and 2,2-dimethylpropanal (2.5 mL, 23.0 mmol. 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (3.75 g, 19.9 mmol, 87%, *E*/*Z* = <1:99) as a colourless oil. Spectroscopic data are consistent with those previously reported.[250]

Rf = 0.61 in cyclohexane.

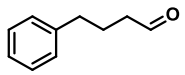
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 5.36 (dt, *J* = 12.0, 1.6 Hz, 1H), 5.22 (dt, *J* = 12.0, 7.3 Hz, 1H), 2.68 (dd, *J* = 9.3, 6.5 Hz, 2H), 2.55 – 2.46 (m, 2H), 1.10 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.2, 140.5, 128.6, 128.4, 127.9, 125.9, 77.5, 77.2, 76.8, 36.7, 33.3, 31.3, 30.5.

IR (neat): ν (cm^{-1}) 2955.3, 1604.3, 1454.7, 1361.8, 1204.4, 1079.2, 1029.8, 906.2.

HRMS (ESI): Calcd for $C_{14}H_{20}Ag$ $[M+Ag]^+$: 295.0610, found 295.0610.

4-Phenylbutanal (**3.15**)



A solution of DMSO (10.3 mL, 145 mmol, 2.2 equiv) in dry DCM (66 mL) was added dropwise to a solution of oxalyl chloride (7.0 mL, 73.9 mmol, 1.12 equiv) in dry DCM (158 mL) that was cooled to −55 °C. After stirring for 5 min, a solution of 4-phenylbutanol (10.2 mL, 66.0 mmol, 1.0 equiv) in DCM (26 mL) was added dropwise. After additional 15 min of stirring, triethylamine (45.7 mL, 33.0 mmol, 5.0 equiv) was added to the reaction mixture, which was then allowed to warm to 25 °C and aqueous HCl (1.0 M, 200 mL) was added. The aqueous phase was extracted with DCM (3 x 250 mL) and the combined organic phase was washed with brine (200 mL) first and then dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain 4-phenylbutanal (9.77 g, 66.0 mmol, quant.) as a colourless oil. Spectroscopic data are consistent with those previously reported.[251]

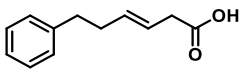
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 9.76 (t, *J* = 1.6 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 2.66 (t, *J* = 7.52 Hz, 2H), 2.45 (td, *J* = 7.3 Hz, *J* = 1.6 Hz, 2H), 1.97 (tt, *J* = 7.5 Hz, *J* = 7.3 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 202.5, 141.4, 128.7, 126.3, 43.3, 35.2, 23.8.

IR (neat): ν (cm^{-1}) 3027, 2936, 2824, 2722, 1721, 1603, 1496, 1454, 1166, 1073, 912, 747, 699.

HRMS (ESI): Calcd for $C_{10}H_{12}ONH_4$ ($[M+NH_4]^+$): 166.1226, found 166.1224.

(*E*)-6-Phenyl-3-hexenoic acid (**3.16**)



Prepared according to a reported procedure.[252] Malonic acid (7.54 g, 72.5 mmol, 1.1 equiv) and *N*-methylmorpholine (8.0 mL, 72.5 mmol, 1.1 equiv) were added to 4-phenylbutanal (**3.15**, 9.77 g, 65.9 mmol, 1.0 equiv). The reaction mixture was heated to 95 °C for 14 h and then

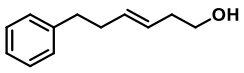
allowed to cool to 25 °C. A solution of H_2SO_4 (11 %, 55 mL) was added and the mixture was stirred for additional 30 min. The aqueous phase was then extracted with DCM (3 x 60 mL) and the combined organic phase was washed with water (80 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by FCC (30% EtOAc in cyclohexane) to obtain (*E*)-6-phenyl-3-hexenoic acid (5.51 g, 29.0 mmol, 44%) as a yellow oil. Spectroscopic data are consistent with those previously reported.[252]

Rf = 0.4 (30% EtOAc in Cy).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.27 (m, 2H), 7.21 – 7.17 (m, 3H), 5.69 – 5.62 (m, 1H), 5.60 – 5.53 (m, 1H), 3.10 – 3.08 (m, 2H), 2.73 – 2.69 (m, 2H), 2.41 – 2.35 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 178.2, 141.8, 134.6, 128.6, 128.5, 126.0, 121.6, 37.8, 35.7, 34.4.

(*E*)-6-Phenyl-3-hexenol (**3.17**)



A solution of (*E*)-6-phenyl-3-hexenoic acid (**3.16**, 5.51 g, 29.0 mmol, 1.0 equiv) in THF (16 mL) was added dropwise to a solution of $LiAlH_4$ (1.65 g, 43.5 mmol, 1.5 equiv) in THF (16 mL) that was cooled to 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 3 h. Et_2O (25 mL) was added and the mixture was cooled to 0 °C. Water (1.7 mL), aqueous NaOH (1.0 M, 1.7 mL) and water (5.1 mL) again were added sequentially and the reaction mixture was stirred at 25 °C for 15 min. $MgSO_4$ was added and the mixture was further stirred for 15 min, then it was filtrated and the filtered solution was reduced *in vacuo*. (*E*)-6-phenyl-3-hexenol (4.59 g, 26.0 mmol, 90%) was obtained as a yellow oil. Spectroscopic data are consistent with those previously reported.[253]

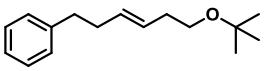
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 5.62 – 5.55 (m, 1H), 5.42 – 5.34 (m, 1H), 3.58 (t, *J* = 6.23 Hz, 2H), 2.73 – 2.69 (m, 2H), 2.40 – 2.34 (m, 2H), 2.27 – 2.22 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 141.9, 133.1, 128.5, 128.4, 126.9, 125.9, 62.0, 36.0, 35.9, 34.5.

IR (neat): ν (cm^{-1}) 3332, 3027, 2927, 1604, 1453, 1045, 969, 744, 697.

HRMS (ESI): Calcd for $C_{12}H_{16}ONa$ ($[M+Na]^+$): 199.1093, found 199.1093.

(*E*)-(6-(*tert*-Butoxy)hex-3-en-1-yl)benzene (**3.1b**)



Prepared according to an adapted reported procedure.[245] Anhydrous magnesium perchlorate (685 mg, 2.84 mmol, 0.1 equiv) was first dried *in vacuo* while heating using a heat gun and then was dissolved with (*E*)-6-phenyl-3-hexenol (**3.17**, 5.01 g, 28.4 mmol, 1.0 equiv) in dichloromethane (42.6 mL). Di-*tert*-butyl dicarbonate (14 mL, 65.3 mmol, 2.3 equiv) was added and the reaction mixture was then stirred under reflux for 14 h. The mixture was first allowed to cool to 25 °C and water (50 mL) was added. The aqueous phase was extracted with DCM (3 x 50 mL) and then the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by FCC (2.5% Et_2O in PET) to obtain (*E*)-*tert*-buxoxy-6-phenyl-3-hexene (6.00 g, 25.8 mmol, 91%) as a colourless oil.

Rf = 0.37 (2.5% Et_2O in PET).

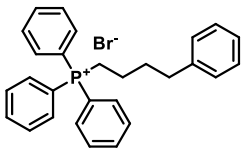
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.27 (m, 2H), 7.21 – 7.17 (m, 3H), 5.60 – 5.53 (m, 1H), 5.51 – 5.43 (m, 1H), 3.34 (t, *J* = 7.19 Hz, 2H), 2.71 – 2.67 (m, 2H), 2.36 – 2.30 (m, 2H), 2.26 – 2.20 (m, 2H), 1.20 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.2, 131.3, 128.6, 128.5, 128.3, 128.3, 127.5, 125.8, 72.7, 61.8, 36.1, 34.6, 34.1, 27.7.

IR (neat): ν (cm^{-1}) 2973, 2930, 1740, 1604, 1454, 1362, 1196, 1078, 968, 879, 744, 698.

HRMS (ESI): Calcd for $C_{16}H_{24}ONa$ ($[M+Na]^+$): 255.1719, found 255.1721.

(4-Phenylbutyl)-triphenylphosphonium bromide (**3.13b**)



A mixture of triphenylphosphine (7.58 g, 28.9 mmol, 1.0 equiv) and 1-bromo-4-phenylbutane (5.1 mL, 28.9 mmol, 1.0 equiv) in toluene (36 mL) was stirred under reflux for 62 h. The reaction mixture was then allowed to cool to 25 °C and the precipitate was filtered and washed with Et_2O to obtain (4-phenylbutyl)-triphenylphosphonium bromide (12.6 g, 26.4 mmol, 91%) as a white powder. Spectroscopic data are consistent with those previously reported.[254]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1H NMR (400 MHz, CDCl3) δ 7.82 – 7.69 (m, 9H), 7.69 – 7.59 (m, 6H), 7.19 – 7.11 (m, 2H), 7.11 – 7.02 (m, 3H), 3.85 – 3.61 (m, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 1.96 (tt, *J* = 7.5 Hz, 2H), 1.66 – 1.53 (m, 2H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 141.2, 135.0 (d, *J* = 3.0 Hz), 133.7 (d, *J* = 10.0 Hz), 130.5 (d, *J* = 12.6 Hz), 128.4 (d, *J* = 18.4 Hz), 125.9, 118.7, 117.8, 34.7, 31.2 (d, *J* = 15.7 Hz), 22.6 (d, *J* = 50.0 Hz), 21.7 (d, *J* = 4.6 Hz).

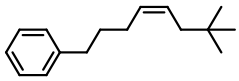
$^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) 24.31.

IR (neat): ν (cm^{-1}) 3414.4, 3054.0, 2932.5, 2863.6, 1486.1, 1438.2, 1112.0, 996.0, 748.5, 691.9.

MP 166.4 °C.

HRMS (ESI): Calcd for $C_{28}H_{28}P$ $[M-Br]^+$: 395.1923, found 395.1928.

(*Z*)-(7,7-Dimethyloct-4-en-1-yl)benzene (**3.1c**)



The title compound was following general procedure **F** from (4-phenylbutyl)-triphenylphosphonium bromide (**3.13b**, 2.05 g mg, 4.31 mmol, 1.0 equiv) and 3,3-dimethylbutanal (541 µL, 4.31 mmol. 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (7,7-dimethyloct-4-en-1-yl)benzene (785 mg, 3.63 mmol, 84%, *E*/*Z* = 25:75) as a colourless oil.

Rf = 0.6 (cyclohexane).

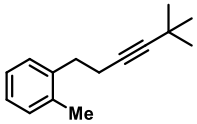
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (m, 2H), 7.24 – 7.18 (m, 3H), 5.56 – 5.42 (m, 2H), 2.65 (m, 2H), 2.14 – 2.05 (m, 2H), 1.96 – 1.87 (m, 2H), 1.76 – 1.66 (m, 2H), 0.91 (*Z-maj*, s, 9H), 0.90 (*E-min*, s).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.8 (*E-min*), 142.7 (*Z-maj*), 132.3 (*E-min*), 130.9 (*Z-maj*), 128.6 (*E-min*), 128.6, 128.4, 128.0 (*E-min*), 127.3, 125.8 (*Z-maj*), 125.8 (*E-min*), 77.5, 77.2, 76.8, 47.3, 41.3, 35.7, 35.5, 32.4, 31.7, 31.6, 31.4, 31.0, 29.4, 27.0.

IR (neat): ν (cm^{-1}) 3027.0, 2951.6, 1604.1, 1455.3, 1240.7, 1030.3, 970.6, 906.8, 744.4, 697.3.

HRMS (ESI): Calcd for $C_{16}H_{24}Ag$ $[M+Ag]^+$: 323.0923, found 323.0922.

1-(5,5-Dimethylhex-3-yn-1-yl)-2-methylbenzene (**3.20a**)



The tile compound was obtained following general procedure **G** from 2-methylphenethyl bromide (0.85 mL. 5.00 mmol, 1.0 equiv) and *t*-butylacetylene (0.8 mL, 6.50 mmol, 1.3 equiv).

The crude product was purified by FCC (cyclohexane) to obtain 1-(5,5-dimethylhex-3-yn-1-yl)-2-methylbenzene (474 mg, 2.40 mmol, 47%) as a colourless oil.

Rf = 0.45 (cyclohexane).

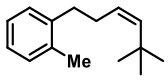
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 – 7.12 (m, 4H), 2.81 (t, *J* = 7.7 Hz, 2H), 2.41 (t, *J* = 7.7 Hz, 2H), 2.35 (s, 3H), 1.20 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 139.4, 136.1, 130.2, 129.3, 126.4, 126.0, 78.0, 33.1, 31.4, 27.5, 19.9, 19.5.

IR (neat): ν (cm^{-1}) 2967.0, 1605.0, 1457.1, 1268.0, 1204.7, 1051.1, 909.9, 741.1, 650.6.

HRMS (ESI): Calcd for $C_{15}H_{20}Ag$ $[M+Ag]^+$: 307.0610, found 307.0616.

(Z)-1-(5,5-Dimethylhex-3-en-1-yl)-2-methylbenzene (**3.1d**)



The title compound was obtained following general procedure **I** from 1-(5,5-dimethylhex-3-yn-1-yl)-2-methylbenzene (**3.20a**, 459 mg, 2.29 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain *(Z)*-1-(5,5-dimethylhex-3-en-1-yl)-2-methylbenzene (330 mg, 1.63 mmol, 71%, *E*/*Z* =<1:99) as a colourless oil.

Rf = 0.82 (cyclohexane).

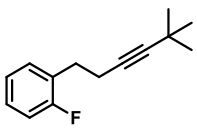
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 – 7.08 (m, 4H), 5.39 (dt, *J* = 12.0, 1.6 Hz, 1H), 5.26 (dt, *J* = 11.9, 7.3 Hz, 1H), 2.71 – 2.64 (m, 2H), 2.52 – 2.43 (m, 2H), 2.34 (s, 3H), 1.12 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 140.5, 140.4, 136.0, 130.3, 129.0, 128.1, 126.1, 126.1, 33.94, 33.3, 31.3, 29.2, 27.1, 19.5.

IR (neat): ν (cm^{-1}) 2955.3, 1461.2, 1361.8, 1204.6, 1054.4, 908.6, 731.0.

HRMS (ESI): Calcd for $C_{15}H_{22}Ag$ $[M+Ag]^+$: 309.0767, found 309.0772.

1-(5,5-Dimethylhex-3-yn-1-yl)-2-fluorobenzene (**3.20b**)



The tile compound was obtained following general procedure **G** from 1-(2-bromoethyl)-2-fluorobenzene (0.70 mL. 5.00 mmol, 1.0 equiv) and *t*-butylacetylene (0.8 mL, 6.50 mmol, 1.3

equiv). The crude product was purified by FCC (cyclohexane) to obtain 1-(5,5-dimethylhex-3-yn-1-yl)-2-fluorobenzene (334 mg, 1.64 mmol, 33%) as a colourless oil.

Rf = 0.4 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27 – 7.13 (m, 2H), 7.09 – 6.94 (m, 2H), 2.82 (t, *J* = 7.9 Hz, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.16 (s, 9H).

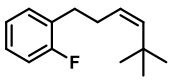
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 161.3 (d, *J* = 245.0 Hz), 131.2 (d, *J* = 5.0 Hz), 128.0 (d, *J* = 8.1 Hz), 127.9 (d, *J* = 15.9 Hz), 123.8 (d, *J* = 3.6 Hz), 115.2 (d, *J* = 22.1 Hz), 90.1, 77.56, 31.4, 29.0 (d, *J* = 2.2 Hz), 27.4, 19.77 (d, *J* = 1.4 Hz).

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) 118.89.

IR (neat): ν (cm^{-1}) 2967.9, 1585.6, 1492.5, 1361.8, 1230.5, 1100.9, 1064.4, 909.7, 829.0, 753.1, 669.9.

HRMS (ESI): Calcd for $C_{14}H_{17}FAg$ $[M+Ag]^+$: 311.0360, found 311.0357.

(Z)-1-(5,5-Dimethylhex-3-en-1-yl)-2-fluorobenzene (**3.1e**)



The title compound was obtained following general procedure **I** from 1-(5,5-dimethylhex-3-yn-1-yl)-2-fluorobenzene (**3.20b**, 321 mg, 1.57 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-2-fluorobenzene (233 mg, 1.13 mmol, 72%, *E*/*Z* = 32:68) as a colourless oil.

Rf = 0.85 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 – 7.11 (m, 2H), 7.11 – 6.95 (m, 2H), 5.46 – 5.16 (m, 2H), 2.75 – 2.66 (m, 2H), 2.55 – 2.45 (*Z-maj*, m, 2H), 2.29 (*E-min*, dt, *J* = 9.2, 6.6 Hz), 1.08 (*Z-maj*, s, 9H), 0.97 (*E-min*, s).

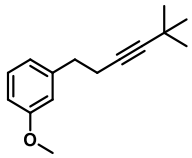
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 160.1 (*Z-maj*, d, *J* = 244 Hz), 160.0 (*E-min*, d, *J* = 244 Hz), 142.7 (*E-min*), 140.8 (*Z-maj*), 130.9 (*E-min*, d, *J* = 5.3 Hz), 130.9 (*Z-maj*, d, *J* = 5.3 Hz), 129.0 (*E-min*, d, *J* = 16 Hz), 129.0 (*Z-maj*, d, *J* = 16 Hz), 127.7 (*Z-maj*, d, *J* = 8.0 Hz), 127.6 (*Z-maj*) , 127.5 (*E-min*, d, *J* = 8.2 Hz), 124.0 (*Z-maj*, d, *J* = 3.6 Hz), 123.8 (*E-min*, d, *J* = 3.6 Hz), 123.6 (*E-min*), 115.3 (*Z-maj*, *J* = 22 Hz), 115.2 (*E-min*, d, *J* = 22 Hz), 33.3, 32.9, 31.2, 29.8.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) 118.82 (*Z-maj*), 118.83 (*E-min*).

IR (neat): ν (cm^{-1}) 2955.9, 1585.2, 1492.2, 1362.3, 1229.5, 1102.2, 1035.1, 972.4, 909.0, 847.6.

HRMS (ESI): Calcd for $C_{14}H_{19}FAg$ $[M+Ag]^+$: 313.0516, found 313.0511.

1-(5,5-Dimethylhex-3-yn-1-yl)-3-methoxybenzene (**3.20c**)



The tile compound was obtained following general procedure **G** from 1-(2-bromoethyl)-3-methoxybenzene (1.1 mL. 7.00 mmol, 1.0 equiv) and *t*-butylacetylene (1.1 mL, 9.10 mmol, 1.3 equiv). The crude product was purified by fractional distillation (84 °C, 0.089 mbar) to obtain 1-(5,5-dimethylhex-3-yn-1-yl)-3-methoxybenzene (595 mg, 2.75 mmol, 39%) as a colourless oil.

Bp: 84 °C, 0.089 mbar.

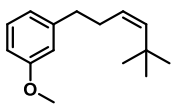
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20 (t, *J* = 7.8 Hz, 1H), 6.85 – 6.72 (m, 3H), 3.80 (s, 3H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.19 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 159.7, 142.9, 129.3, 121.1, 114.4, 111.6, 89.9, 78.0, 55.3, 36.0, 31.5, 27.5, 21.1.

IR (neat): ν (cm^{-1}) 2966.8, 1601.6, 1454.8, 1361.5, 1262.3, 1152.8, 1050.7, 910.1, 870.0, 778.1.

HRMS (ESI): Calcd for $C_{15}H_{20}OAg$ $[M+Ag]^+$: 323.0560, found 323.0656.

(*Z*)-1-(5,5-Dimethylhex-3-en-1-yl)-3-methoxybenzene (**3.1f**)



The title compound was obtained following general procedure **I** from 1-(5,5-dimethylhex-3-yn-1-yl)-3-methoxybenzene (**3.20c**, 569 mg, 2.63 mmol, 1.0 equiv). The crude product was purified by FCC (1% EtOAc in cyclohexane) to obtain (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-3-methoxybenzene (456 mg, 2.09 mmol, 79%, *E*/*Z* = 5:95) as a colourless oil.

Rf = 0.25 (1% EtOAc in Cy).

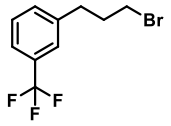
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 (t, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.79 – 6.72 (m, 2H), 5.36 (dt, *J* = 11.9, 1.6 Hz, 1H), 5.22 (dt, *J* = 12.0, 7.2 Hz, 1H), 3.81 (s, 3H), 2.70 – 2.62 (m, 2H), 2.56 – 2.46 (m, 2H), 1.11 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 159.7, 143.9, 140.5, 129.4, 127.8, 121.0, 114.4, 111.1, 55.3, 36.7, 33.3, 31.2, 30.4.

IR (neat): ν (cm^{-1}) 2953.8, 1600.9, 1464.0, 1261.3, 1152.1, 1046.0, 873.5, 775.3.

HRMS (ESI): Calcd for $C_{15}H_{22}OAg$ $[M+Ag]^+$: 325.0716, found 325.0722.

1-(3-Bromopropyl)-3-(trifluoromethyl)benzene (**3.19a**)



PPh_3 (3.15 g, 12.0 mmol, 1.2 equiv) was added portionwise to a solution of 3-(3-(trifluoromethyl)phenyl)propan-1-ol (2.04 g, 10.0 mmol, 1.0 equiv) and CBr_4 (3.98g, 12.0 mmol, 1.2 equiv) in DCM (20.0 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. The reaction mixture was then filtered over Celite® and the volatiles removed under reduced pressure. The crude product was purified by FCC (cyclohexane) to obtain 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (2.51 g, 9.39 mmol, 94%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[255]

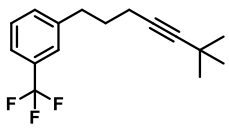
Rf = 0.4 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.51 – 7.44 (m, 2H), 7.44 – 7.37 (m, 2H), 3.40 (t, *J* = 6.5 Hz, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.24 – 2.14 (m, 2H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 141.6, 132.1 (q, *J* = 1.4 Hz), 131.0 (q, *J* = 32.0 Hz), 125.3 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 204.2 Hz), 123.3 (q, *J* = 3.7 Hz), 34.0, 33.9, 32.8.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.60.

1-(6,6-Dimethylhept-4-yn-1-yl)-3-(trifluoromethyl)benzene (**3.20d**)



The title product was obtained following general procedure **H** from 1-(3-bromopropyl)-3-(trifluoromethyl)benzene (**3.19a**, 0.93 mL, 5.00 mmol, 1.0 equiv), and *t*-butylacetylene (0.8 mL, 6.5 mmol, 1.3 equiv). The crude product was purified by FCC (cyclohexane) to obtain 1-(6,6-dimethylhept-4-yn-1-yl)-3-(trifluoromethyl)benzene (765 mg, 2.85 mmol, 57%) as a colourless oil.

Rf = 0.5 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.49 – 7.42 (m, 2H), 7.42 – 7.34 (m, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.16 (t, *J* = 6.9 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.22 (s, 9H).

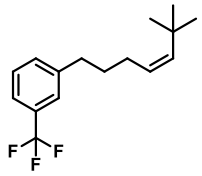
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 143.0, 132.1 (q, *J* = 1.4 Hz), 130.8 (q, *J* = 31.9 Hz), 128.9, 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 272 Hz), 122.9 (q, *J* = 3.9 Hz), 90.2, 77.7, 34.6, 31.5, 30.6, 27.5, 18.2.

$^{19}F\{^{1}H\}$-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.58.

IR (neat): ν (cm^{-1}) 2969.1, 1451.5, 1327.7, 1123.5, 1073.2, 898.6, 798.9, 702.1, 662.1.

HRMS (ESI): Calcd for $C_{16}H_{19}F_3Ag$ $[M+Ag]^+$: 375.0484, found 375.0483.

(*Z*)-1-(6,6-Dimethylhept-4-en-1-yl)-3-(trifluoromethyl)benzene (**3.1g**)



The title compound was obtained following general procedure **I** from 1-(6,6-dimethylhept-4-yn-1-yl)-3-(trifluoromethyl)benzene (**3.20d**, 751 mg, 2.80 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-1-(6,6-dimethylhept-4-en-1-yl)-3-(trifluoromethyl)benzene (736 mg, 2.72 mmol, 97%, *E*/*Z* = 9:91) as a colourless oil.

Rf = 0.8 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.47 – 7.42 (m, 2H), 7.42 – 7.36 (m, 1H), 7.39 – 7.34 (m, 1H), 5.45 (*E-min*, dt, *J* = 15.6, 1.3 Hz), 5.36 (*Z-maj*, dt, *J* = 12.0, 1.8 Hz, 1H), 5.17 (dt, *J* = 12.0, 7.4 Hz, 1H), 2.70 (*Z-maj*, d, *J* = 8.0 Hz, 2H), 2.66 (*E-min*, t, *J* = 7.8 Hz), 2.23 (*Z-maj*, m, 2H), 2.06 – 2.00 (*E-min*, m), 1.76 – 1.66 (m, 2H), 1.09 (*Z-maj*, s, 9H), 1.00 (*E-min*, s).

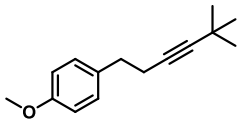
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 143.5, 140.7, 132.0 (q, *J* = 1.4 Hz), 130.7 (q, *J* = 31.9 Hz), 128.8, 128.0, 125.3 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 272 Hz), 122.8 (q, *J* = 3.9 Hz), 35.5, 33.3, 31.9, 31.2, 29.9.

$^{19}F\{^{1}H\}$-NMR (470 MHz, $CDCl_3$): δ (ppm) -62.55 (*E-min*, s, 1F), -62.57 (*Z-maj*, s, 1F).

IR (neat): ν (cm^{-1}) 2955.1, 1450.7, 1328.9, 1123.7, 1073.2, 899.3, 798.5, 701.4.

HRMS (ESI): Calcd for $C_{16}H_{21}F_3Ag$ $[M+Ag]^+$: 377.0641, found 377.0642.

1-(5,5-Dimethylhex-3-yn-1-yl)-4-methoxybenzene (**3.20e**)



The tile compound was obtained following general procedure **G** from 1-(2-bromoethyl)-4-methoxybenzene (1.1 mL. 7.00 mmol, 1.0 equiv) and *t*-butylacetylene (1.1 mL, 9.10 mmol, 1.3 equiv). The crude product was purified by fractional distillation (79 °C, 0.078 mbar) to obtain 1-(5,5-dimethylhex-3-yn-1-yl)-4-methoxybenzene (733 mg, 3.39 mmol, 48%) as a colourless oil.

Bp: 79 °C, 0.078 mbar.

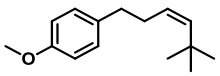
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19 – 7.11 (m, 2H), 6.87 – 6.79 (m, 2H), 3.79 (s, 3H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 1.19 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.1, 133.4, 129.7, 113.7, 89.9, 78.1, 55.4, 35.0, 31.5, 27.5, 21.5.

IR (neat): ν (cm^{-1}) 2966.8, 1612.8, 1512.1, 1458.1, 1361.4, 1244.8, 1177.5, 1107.4, 1037.7, 910.3, 82..9, 733.4.

HRMS (ESI): Calcd for $C_{15}H_{20}OAg$ $[M+Ag]^+$: 323.0560, found 323.0560.

(*Z*)-1-(5,5-Dimethylhex-3-en-1-yl)-4-methoxybenzene (**3.1h**)



The title compound was obtained following general procedure **I** from 1-(5,5-dimethylhex-3-yn-1-yl)-4-methoxybenzene (**3.20e**, 476 mg, 2.20 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane to 2% EtOAc in cyclohexane) to obtain (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-4-methoxybenzene (480 mg, 2.20 mmol, quant., *E*/*Z* = 1:9) as a colourless oil.

Rf = 0.28 (cyclohexane).

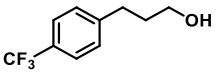
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.18 – 7.06 (m, 2H), 6.90 – 6.80 (m, 2H), 5.46 (*E-min*, dt, *J* = 15.6, 1.1 Hz), 5.35 (*Z-maj*, dt, *J* = 12.0, 1.6 Hz, 1H), 5.21 (dt, *J* = 12.0, 7.3 Hz, 1H), 3.80 (s, 3H), 2.67 – 2.57 (m, 2H), 2.53 – 2.42 (*Z-maj*, m, 2H), 2.30 – 2.23 (*E-min*, m), 1.10 (*Z-maj,* s, 9H), 0.99 (*E-min*, s).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 157.9, 140.4, 134.3, 129.5, 128.0, 113.8, 55.4, 35.7 (*Z-maj*), 35.5 (*E-min*), 35.0, (*E-min*) 33.3 (*Z-maj*), 32.9 (*E-min*), 31.2 (*Z-maj*), 30.7 (*Z-maj*), 29.9 (*E-min*).

IR (neat): ν (cm^{-1}) 2954.1, 1612.5, 1511.8, 1463.5, 1244.3, 1177.3, 1038.5, 909.2, 824.8, 732.3.

HRMS (ESI): Calcd for $C_{15}H_{22}OAg$ $[M+Ag]^+$: 325.0716, found 325.0722.

3-(4-(Trifluoromethyl)phenyl)propan-1-ol (**3.14b**)



A solution of 4-(Trifluoromethyl)hydrocinnamic acid (4.36 g, 20.0 mmol, 1.0 equiv) in anhydrous THF (11.5 mL) was added dropwise to a solution of $LiAlH_4$ (1.14 g, 30.0 mmol, 1.5 equiv) in anhydrous THF (11.5 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. The reaction mixture was then cooled to 0 °C and diluted with Et_2O (30 mL), and then treated sequentially with water (1.2 mL), NaOH (2 M, 2.5 mL), water (3.6 mL), warm to 25 °C and stirred for 15 min. Then a copious amount of $MgSO_4$ was added and the mixture stirred for further 15 min (*Fieser Workup*). The slurry was then filtered to remove the salts and the filtrate was concentrated under reduced pressure to obtain 3-(4-(trifluoromethyl)phenyl)propan-1-ol (4.03 g, 19.9 mmol, 99%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[256]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 – 7.49 (m, 2H), 7.35 – 7.27 (m, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 8.1 Hz, 2H), 1.94 – 1.85 (m, 2H), 1.80 (s, 1H).

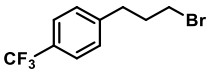
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 146.1 (q, *J* = 1.3 Hz), 128.9, 128.4 (q, *J* = 32.3 Hz), 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.7 Hz), 62.0, 34.0, 32.0.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) 62.30.

IR (neat): ν (cm^{-1}) 3329.3, 2941.6, 1619.2, 1418.7, 1223.3, 1111.6, 1065.1, 911.8, 844.1, 732.9.

HRMS (ESI): Calcd for $C_{10}H_{11}F_3ONa$ $[M+Na]^+$: 227.0654, found 227.0352.

1-(3-Bromopropyl)-4-(trifluoromethyl)benzene (**3.19b**)



PBr_3 (2.40 g, 8.85 mmol, 0.5 equiv) was added portionwise to a solution of 3-(4-(trifluoromethyl)phenyl)propan-1-ol (**3.14b**, 3.64 g, 17.7 mmol, 1.0 equiv) in Et_2O (35.5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 14 h. The reaction mixture was then cooled to 0 °C and quenched sequentially with water (20 mL) and K_2CO_3 (1 M, 20 mL). The organic layer was collected and washed with brine (20 mL), dried over $MgSO_4$ and the concentrated under reduced pressure. The crude product was purified by FCC (cyclohexane) to obtain 1-(3-bromopropyl)-4-(trifluoromethyl)benzene (2.88 g, 10.8 mmol, 61%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[257]

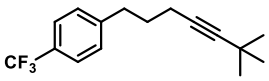
Rf = 0.4 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 – 7.52 (m, 2H), 7.36 – 7.28 (m, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H), 2.18 (tt, *J* = 7.4, 6.4 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 144.8 (q, *J* = 1.4 Hz), 129.0, 128.7 (q, *J* = 32.4 Hz), 125.6 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.8 Hz), 33.9, 33.9, 32.8.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) 62.36.

1-(6,6-Dimethylhept-4-yn-1-yl)-4-(trifluoromethyl)benzene (**3.20f**)



The tile compound was obtained following general procedure **G** from 1-(3-bromopropyl)-4-(trifluoromethyl)benzene (**3.19b**, 0.55 mL. 3.00 mmol, 1.0 equiv) and *t*-butylacetylene (0.48 mL, 3.90 mmol, 1.3 equiv). The crude product was purified by FCC (cyclohexane) to obtain 1-(6,6-dimethylhept-4-yn-1-yl)-4-(trifluoromethyl)benzene (538 mg, 2.00 mmol, 67%) as a colourless oil.

Rf = 0.28 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.51 (m, 2H), 7.33 – 7.28 (m, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 6.9 Hz, 2H), 1.79 (tt, *J* = 7.6, 6.9 Hz, 2H), 1.22 (s, 9H).

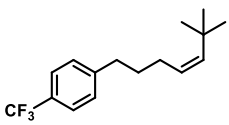
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 146.2 (q, *J* = 1.4 Hz), 129.0, 128.4 (q, *J* = 32.3 Hz), 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.7 Hz), 90.2, 77.7, 34.6, 31.6, 30.6, 27.5, 18.2.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.29.

IR (neat): ν (cm^{-1}) 2968.9, 1619.3, 1323.9, 1122.7, 1067.3, 1019.2, 840.8, 734.4.

HRMS (ESI): Calcd for $C_{16}H_{19}F_3Ag$ $[M+Ag]^+$: 375.0484, found 375.0487.

(*Z*)-1-(6,6-Dimethylhept-4-en-1-yl)-4-(trifluoromethyl)benzene (**3.1i**)



The title compound was obtained following general procedure **I** from 1-(6,6-dimethylhept-4-yn-1-yl)-4-(trifluoromethyl)benzene (**3.20f**, 518 mg, 1.93 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-1-(6,6-dimethylhept-4-en-1-yl)-4-(trifluoromethyl)benzene (513 mg, 1.90 mmol, 98%, *E*/*Z* = 15:85 as a colourless oil.

Rf = 0.96 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.51 (m, 2H), 7.32 – 7.27 (m, 2H), 5.47 (*E-min*, dt, *J* = 15.6, 1.3 Hz), 5.36 (*Z-maj*,z dt, *J* = 12.0, 1.7 Hz, 1H), 5.17 (dt, *J* = 11.9, 7.4 Hz, 1H), 2.69 (*Z-maj,* t, *J* = 7.6 Hz, 2H), 2.66 (*E-min,* t, *J* = 7.7 Hz), 2.23 (tdd, *J* = 7.5, 7.5 1.7 Hz, 2H), 1.74 – 1.64 (m, 2H), 1.09 (*Z-maj,* s, 9H), 1.00 (*E-min*, s).

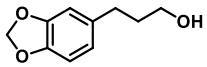
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 147.0 (*E-min*, q, *J* = 1.3 Hz), 146.8 (*Z-maj*, q, *J* = 1.3 Hz), 142.6 (*E-min*), 140.7 (*Z-maj*), 128.9 (*E-min*), 128.9 (*Z-maj*), 128.3 (*Z-maj*, q, *J* = 32.3 Hz), 128.0, 125.3 (*Z-maj*, q, *J* = 3.8 Hz), 124.5 (*Z-maj*, q, *J* = 271 Hz), 124.0, 35.5 (*Z-maj*), 35.3 (*E-min*), 33.3 (*Z-maj*), 33.0 (*E-min*), 32.2 (*E-min*), 31.9 (*Z-maj*), 31.3 (*Z-maj*), 29.9 (*E-min*), 27.9 (*Z-maj*), 27.1 (*E-min*).

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.27 (*E-min*), 62.28 (*Z-maj*).

IR (neat): ν (cm^{-1}) 2954.6, 1619.5, 1462.6, 1416.7, 1323.7, 1122.4, 1067.3, 1019.1, 842.4, 728.7.

HRMS (ESI): Calcd for $C_{16}H_{21}F_3Ag$ $[M+Ag]^+$: 377.0641, found 377.0647.

3-(Benzo-dioxol-5-yl)propan-1-ol (**3.14c**)



A solution of 3-(benzo[d][1,3]dioxol-5-yl)propanoic acid (2.99 g, 15.4 mmol, 1.0 equiv) in anhydrous THF (8.8 mL) was added dropwise to a solution of $LiAlH_4$ (877 mg, 23.1 mmol, 1.5 equiv) in anhydrous THF (8.8 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. The reaction mixture was then cooled to 0 °C and diluted with Et_2O (30 mL), and then treated (*Fieser Workup*) sequentially with water (0.9 mL), NaOH (2 M, 1.9 mL), water (2.7 mL), warm to 25 °C and stir for 15 min. Then a copious amount of $MgSO_4$ was added and the mixture stirred for further 15 min. The slurry was then filtered to remove the salts and the filtrate was concentrated under reduced pressure. The crude product was purified by FCC (40% EtOAc in Cyclohexane) to obtain 3-(benzo-dioxol-5-yl)propan-1-ol (2.71 g, 15.1 mmol, 98%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[258]

Rf = 0.45 (40% EtOAc in Cy).

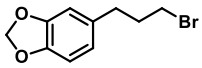
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.73 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.7 Hz, 1H), 6.64 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.91 (s, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.62 (d, *J* = 7.5 Hz, 2H), 1.90 – 1.78 (m, 2H), 1.63 (s, 1H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.7, 145.7, 135.7, 121.2, 109.0, 108.3, 100.9, 62.2, 34.5, 31.9.

IR (neat): ν (cm^{-1}) 3346.5, 2937.7, 2882.0, 1851.8, 1487.2, 1440.7, 1242.1, 1187.3, 1034.0, 927.6, 808.5.

HRMS (ESI): Calcd for $C_{10}H_{12}O_3Na$ $[M+Na]^+$: 203.0679, found 203.0682.

5-(3-Bromopropyl)benzo-1,3-dioxole (**3.19c**)



Triphenylphosphine (4.75 g, 18.1 mmol, 1.2 equiv) was added portionwise to a solution of 3-(benzo-dioxol-5-yl)propan-1-ol (**3.14c**, 2.72 g, 15.1 mmol, 1.0 equiv) and CBr_4 (6.01 g, 18.1 mmol, 1.2 equiv) in dichloromethane (30 mL) at 0 °C. The reaction mixture was then stirred at 25 °C for 14 h. The solids were removed by filtration and the filtrate concentrated under reduced pressure. The crude product was purified by FCC (2% Et_2O in cyclohexane) to obtain 5-(3-bromopropyl)benzo-1,3-dioxole (3.65 g, 15.0 mmol, 99%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[259]

Rf = 0.4 (2% Et_2O in Cy).

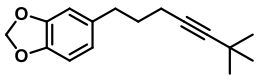
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.74 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.7 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.93 (s, 2H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.70 (t, *J* = 7.3 Hz, 2H), 2.12 (t, *J* = 7.3, 6.6 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.8, 146.0, 134.4, 121.5, 109.1, 108.4, 101.0, 34.5, 33.8, 33.1.

IR (neat): ν (cm^{-1}) 2890.5, 1487.2, 1441.8, 1235.3, 1188.2, 1037.6, 935.5, 807.6, 731.1.

HRMS (ESI): Calcd for $C_{10}H_{11}BrO_2Ag$ $[M+Ag]^+$: 348.8988, found 348.8994.

5-(6,6-Dimethylhept-4-yn-1-yl)benzo-1,3-dioxole (**3.20g**)



The title product was obtained following general procedure **H** from 5-(3-bromopropyl)benzo-1,3-dioxole (**3.19c**, 3.65 g, 15.0 mmol, 1.0 equiv), and *t*-butylacetylene (2.4 mL, 19.5 mmol, 1.3 equiv). The crude product was purified by FCC (2% Et_2O in cyclohexane) to obtain 5-(6,6-dimethylhept-4-yn-1-yl)benzo-1,3-dioxole (1.50 g, 6.14 mmol, 41%) as a colourless oil.

Rf = 0.45 (2% Et_2O in Cy).

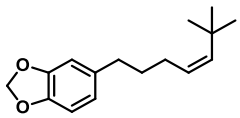
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.73 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.7 Hz, 1H), 6.64 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.14 (t, *J* = 7.0 Hz, 2H), 1.74 (tt, *J* = 7.5, 7.0 Hz, 2H), 1.22 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.6, 145.7, 135.9, 121.4, 109.1, 108.2, 100.9, 89.8, 78.1, 34.5, 31.6, 31.2, 27.5, 18.1.

IR (neat): ν (cm^{-1}) 2966.9, 1488.3, 1441.8, 1361.1, 1242.6, 1188.3, 1040.0, 938.2, 808.1.

HRMS (ESI): Calcd for $C_{16}H_{29}O_2Ag$ $[M+Ag]^+$: 351.0509, found 351.0512.

(*Z*)-5-(6,6-Dimethylhept-4-en-1-yl)benzo-1,3-dioxole (**3.1j**)



The title compound was obtained following general procedure **I** from 5-(6,6-dimethylhept-4-yn-1-yl)benzo-1,3-dioxole (**3.20g**, 977 mg, 4.00 mmol, 1.0 equiv). The crude product was purified by FCC (1% Et_2O in cyclohexane) to obtain (*Z*)-5-(6,6-dimethylhept-4-en-1-yl)benzo-1,3-dioxole (962 mg, 3.90 mmol, 98%, *E*/*Z* = 28:72) as a colourless oil.

Rf = 0.2 (1% Et_2O in Cy).

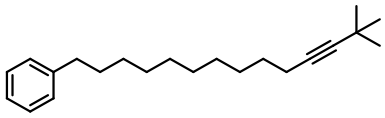
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.73 (d, *J* = 7.9 Hz, 1H), 6.69 – 6.67 (m, 1H), 6.65 – 6.60 (m, 1H), 5.92 (s, 2H), 5.45 (*E-min*, dt, *J* = 15.6, 1.3 Hz), 5.38 – 5.25 (m, 1H), 5.17 (*Z-maj*, dt, *J* = 12.0, 7.3 Hz, 1H), 2.60 – 2.48 (m, 2H), 2.26 – 2.15 (*Z-maj*, m, 2H), 2.05 – 1.95 (*E-min*, m), 1.70 – 1.56 (m, 2H), 1.09 (*Z-maj*, s, 9H), 0.99 (*E-min*, s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.6 (*Z-maj*), 147.6 (*E-min*), 145.6 (*Z-maj*), 145.5 (*E-min*), 142.2 (*E-min*), 140.3 (*Z-maj*), 136.7 (*E-min*), 136.5 (*Z-maj*), 128.5 (*Z-maj*), 124.3 (*E-min*), 121.3 (*E-min*), 121.2 (*Z-maj*), 109.1 (*E-min*), 109.0 (*Z-maj*), 108.2 (*Z-maj*), 108.2 (*E-min*), 100.8 (*Z-maj*), 100.8 (*E-min*), 35.5 (*Z-maj*), 35.2 (*E-min*), 33.3 (*Z-maj*), 32.9 (*E-min*), 32.4 (*Z-maj*), 32.1 (*E-min*), 31.8 (*E-min*), 31.3 (*Z-maj*), 30.0 (*E-min*), 28.0 (*Z-maj*).

IR (neat): ν (cm^{-1}) 2953.8, 1488.1, 1441.8, 1361.5, 1242.8, 1188.3, 1040.6, 939.1, 807.9, 732.7.

HRMS (ESI): Calcd for $C_{16}H_{22}O_2Ag$ $[M+Ag]^+$: 353.0665, found 353.0670.

(13,13-Dimethyltetradec-11-yn-1-yl)benzene (**3.20h**)



The title product was obtained following general procedure **H** from (10-bromodecyl)benzene (963 mg, 3.24 mmol, 1.0 equiv), and *t*-butylacetylene (0.62 mL, 4.21 mmol, 1.3 equiv). The crude product was purified by FCC (cyclohexane) to obtain (13,13-dimethyltetradec-11-yn-1-yl)benzene (770 mg, 2.58 mmol, 80%) as a colourless oil.

Rf = 0.4 (cyclohexane).

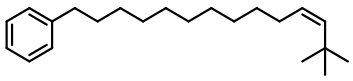
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.12 (t, *J* = 7.1 Hz, 2H), 1.67 – 1.55 (m, 2H), 1.50 – 1.40 (m, 2H), 1.38 – 1.23 (m, 12H), 1.19 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 143.1, 128.5, 128.4, 125.7, 89.1, 78.7, 77.5, 77.2, 76.8, 36.1, 31.7, 31.6, 29.7, 29.7, 29.7, 29.5, 29.4, 29.3, 28.9, 27.5, 18.8.

IR (neat): ν (cm^{-1}) 2926.1, 2854.9, 1455.2, 1361.4, 1265.5, 1205.0, 909.1, 733.2.

HRMS (ESI): Calcd for $C_{22}H_{34}Ag$ $[M+Ag]^+$: 405.1706, found 405.1705.

(*Z*)-(13,13-Dimethyltetradec-11-en-1-yl)benzene (**3.1k**)



The title compound was obtained following general procedure **I** from (13,13-dimethyltetradec-11-yn-1-yl)benzene (**3.20h**, 740 mg, 2.48 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-(13,13-dimethyltetradec-11-en-1-yl)benzene (693 mg, 2.31 mmol, 93%, *E*/*Z* = 26:74) as a colourless oil.

Rf = 0.88 (cyclohexane).

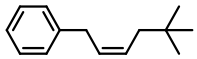
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.22 (m, 2H), 7.22 – 7.13 (m, 3H), 5.42 (*E-min*, dt, *J* = 15.6, 1.3 Hz), 5.34 – 5.24 (m, 1H), 5.15 (dt, *J* = 11.9, 7.3 Hz, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.20 – 2.09 (*Z-maj*, m, 2H), 2.01 – 1.92 (*E-min*, m), 1.66 – 1.54 (m, 2H), 1.37 – 1.21 (m, 14H), 1.10 (*Z-maj*, s, 9H), 0.98 (*E-min*, s).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 143.1, 141.6, 139.7, 129.3, 128.5, 128.4, 125.7, 124.9, 36.2, 33.2, 32.9, 32.8, 31.7, 31.4, 30.5, 30.0, 29.9, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.3, 28.5.

IR (neat): ν (cm^{-1}) 2924.4, 2854.0, 1460.2, 1361.7, 1204.0, 1029.8, 971.7, 908.6.

HRMS (ESI): Calcd for $C_{22}H_{36}Ag$ $[M+Ag]^+$: 407.1862, found 407.1858.

(*Z*)-(5,5-Dimethylhex-2-en-1-yl)benzene (**3.1l**)



The title compound was obtained following general procedure **F** from (2-phenylethyl)-triphenylphosphonium bromide (2.30 g, 5.16 mmol, 1.0 equiv) and 3,3-dimethylbutanal (648 µL, 5.16 mmol, 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (*Z*)-(5,5-dimethylhex-2-en-1-yl)benzene (661 mg, 3.51 mmol, 68%, *E*/*Z* = 23:77) as a colourless oil.

Rf = 0.62 (cyclohexane).

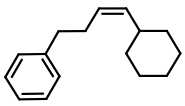
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 5.73 – 5.54 (m, 2H), 3.43 (*Z-maj*, d, *J* = 6.6 Hz, 2H), 3.38 (*E-min,* d, *J* = 4.5 Hz), 2.12 – 2.05 (*Z-maj*, m, 2H), 1.93 (*E-min*, d, *J* = 4.3 Hz), 0.96 (*Z-maj*, s, 9H), 0.91 (*E-min*,s).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 141.4 (*Z-maj*), 141.3 (*E-min*), 131.1 (*E-min*), 129.6 (*Z-maj*), 129.2 (*E-min*), 128.6 (*E-min*), 128.5 (*Z-maj*), 128.5 (*Z-maj*), 128.5 (*E-min*), 127.9 (*Z-maj*), 126.0 (*E-min*), 125.9 (*Z-maj*), 77.5 (*E-min*), 77.2 (*E-min*), 76.8 (*E-min*), 47.2 (*E-min*), 41.3 (*Z-maj*), 39.4 (*E-min*), 33.7 (*Z-maj*), 31.5(*Z-maj*), 31.1 (*E-min*), 29.5(*Z-maj*), 29.5 (*E-min*).

IR (neat): ν (cm^{-1}) 3026.1, 2954.0, 1603.0, 1472.1, 1364.2, 1240.1, 908.5, 734.4, 696.5.

HRMS (ESI): Calcd for $C_{14}H_{20}Ag$ ($[M+Ag]^+$): 295.0610, found 295.0613.

(*Z*)-(4-Cyclohexylbut-3-en-1-yl)benzene (**3.1m**)



The title compound was obtained following general procedure **F** from (3-phenylpropyl)-triphenylphosphonium bromide (923 mg, 2.00 mmol, 1.0 equiv) and cyclohexanal (242 µL, 2.00 mmol. 1.0 equiv). The crude product was purified by FCC (cyclohexane) to obtain (4-cyclohexylbut-3-en-1-yl)benzene (408 mg, 1.90 mmol, 95%, *E*/*Z* = 10:90) as a colourless oil. Spectroscopic data are consistent with those previously reported.[260]

Rf = 0.65 (cyclohexane).

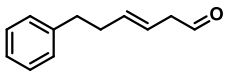
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 5.42 – 5.17 (m, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.41 – 2.25 (m, 2H), 2.24 – 2.11 (m, 1H), 1.71 – 1.45 (m, 5H), 1.30 – 0.94 (m, 5H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.4 (*E-min*), 142.3 (*Z-maj*), 137.3 (*E-min*), 136.9 (*Z-maj*), 128.6 (*E-min*), 128.6 (*Z-maj*), 128.4 (*Z-maj*), 128.3 (*E-min*), 126.9 (*Z-maj*), 126.8 (*E-min*), 125.9 (*Z-maj*), 125.8 (*E-min*), 40.8 (*E-min*), 36.5 (*Z-maj*), 36.5 (*Z-maj*), 36.4 (*E-min*), 34.7 (*E-min*), 33.4 (*Z-maj*), 33.3 (*E-min*), 29.5 (*Z-maj*), 26.4 (*E-min*), 26.3 (*E-min*), 26.2 (*Z-maj*), 26.1 (*Z-maj*).

IR (neat): ν (cm^{-1}) 3024.9, 2950.7, 1600.9, 1364.3, 1249.1, 907.6, 729.9, 649.6.

HRMS (ESI): Calcd for $C_{21}H_{28}Ag$ $[M+Ag]^+$: 387.1236, found 387.1232.

(*E*)-6-Phenylhex-3-enal (**3.21**)



(*E*)-6-Phenyl-3-hexenol (**3.17**, 0.9 mL, 5.00 mmol, 1.0 equiv) was added to a solution of Dess-Martin Periodinane (2.55 g, 6.00 mmol, 1.2 equiv) and water (104 µL, 5.75 mmol, 1.15 equiv) in dichloromethane (32 mL). The reaction mixture was stirred for 1 h and then carefully quenched with sat. aq. $NaHCO_3$ (25 mL) and washed with sat. aq. $Na_2S_2O_3$ (3 x 25 mL). The organic layer was then dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (5% EtOAc in cyclohexane to 10% EtOAc in cyclohexane) to obtain (*E*)-6-phenylhex-3-enal (316 mg, 1.82 mmol, 63%) as a colourless oil.

Rf = 0.3 (10% EtOAc in Cy).

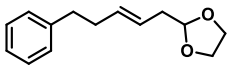
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 9.63 (t, *J* = 2.0 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.24 – 7.14 (m, 3H), 5.72 – 5.60 (m, 1H), 5.60 – 5.48 (m, 1H), 3.16 – 3.08 (m, 2H), 2.71 (t, *J* = 7.8 Hz, 2H), 2.45 – 2.34 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 200.4, 141.7, 135.9, 128.6, 128.5, 126.0, 120.1, 47.4, 35.7, 34.6.

IR (neat): ν (cm^{-1}) 3027.3, 2925.6, 1722.0, 1495.7, 1453.5, 970.7, 909.2, 730.7.

HRMS (ESI): Calcd for $C_{12}H_{14}ONa$ $[M+Na]^+$: 197.0937, found 197.0937.

(*E*)-2-(5-Phenylpent-2-en-1-yl)-1,3-dioxolane (**3.1n**)



Performed according to an adapted literature procedure.[261] Tetra-n-butylammonium tribromide (89.1 mg, 0.181 mmol, 0.1 equiv) was added to a solution of (*E*)-6-phenylhex-3-enal (**3.21**, 315 mg, 1.81 mmol, 1.0 equiv) and ethyl orthoformate (0.33 mL, 1.99 mmol, 1.1 equiv) in ethylene glycol (0.37 mL, 7.24 mmol, 4.0 equiv). The reaction mixture was stirred at 25 °C for 14 h and then diluted with Et_2O (25 mL) and quenched with sat. aq. $NaHCO_3$ (25 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL), the combined organic layers were dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (2.5% EtOAc in cyclohexane) to obtain (*E*)-2-(5-phenylpent-2-en-1-yl)-1,3-dioxolane (290 mg, 1.33 mmol, 73%) as a colourless oil.

Rf = 0.18 (2.5% EtOAc in Cy).

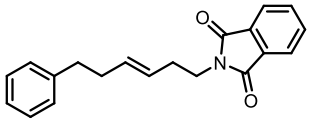
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 – 7.25 (m, 2H), 7.20 – 7.15 (m, 3H), 5.68 – 5.56 (m, 1H), 5.53 – 5.42 (m, 1H), 4.86 (t, *J* = 4.8 Hz, 1H), 4.00 – 3.92 (m, 2H), 3.89 – 3.80 (m, 2H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.39 – 2.31 (m, 4H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.1, 133.5, 128.6, 128.4, 125.9, 124.2, 104.3, 65.1, 37.6, 35.9, 34.6.

IR (neat): ν (cm^{-1}) 2929.7, 2884.5, 1603.9, 1453.9, 1398.5, 1134.8, 1036.8, 970.1, 746.2, 699.2.

HRMS (ESI): Calcd for $C_{14}H_{18}O_2Ag$ $[M+Ag]^+$: 325.0352, found 325.0358.

(*E*)-2-(6-Phenylhex-3-en-1-yl)isoindoline-1,3-dione (**3.1o**)



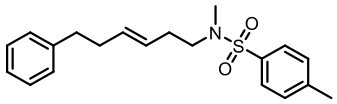
Diisopropyl azodicarboxylate (0.77 mL, 3.90 mmol, 1.3 equiv) was added dropwise to a solution of (*E*)-6-Phenyl-3-hexenol (**3.17**, 529 mg, 3.00 mmol, 1.0 equiv), phtalimide (0.47 mL, 3.90 mmol, 1.3 equiv) and triphenylphosphine (1.02 g, 3.90 mmol, 1.3 equiv) in THF (33 mL) and the mixture was stirred at 25 °C for 4 h. The reaction mixture was then quenched with water (30 mL) and the aqueous layer extracted with DCM (3 x 30 mL), the combined organic layers dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (25% EtOAc in cyclohexane) to obtain (*E*)-2-(6-phenylhex-3-en-1-yl)isoindoline-1,3-dione (646 mg, 2.12 mmol, 71%) as a white solid. Spectroscopic data are consistent with those previously reported.[262]

Rf = 0.3 (25% EtOAc in Cy)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 – 7.80 (m, 2H), 7.75 – 7.66 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 – 7.11 (m, 1H), 7.11 – 7.04 (m, 2H), 5.63 – 5.34 (m, 2H), 3.71 (t, *J* = 7.1 Hz, 2H), 2.54 (t, *J* = 9.1, 6.6 Hz, 2H), 2.42 – 2.32 (m, 2H), 2.30 – 2.21 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 168.5, 142.0, 134.0, 132.9, 132.3, 128.5, 128.4, 126.6, 125.9, 123.3, 37.9, 35.9, 34.5, 31.8.

(*E*)-*N*,4-Dimethyl-N-(6-phenylhex-3-en-1-yl)benzenesulfonamide (**3.1p**)



Diisopropyl azodicarboxylate (0.78mL, 3.99 mmol, 1.1 equiv) was added dropwise to a solution of (*E*)-6-Phenyl-3-hexenol (**3.17**, 640 mg, 3.63 mmol, 1.0 equiv), N-methyl-p-toluenesulfonamide (672 mg, 3.63 mmol, 1.0 equiv) and triphenylphosphine (1.05 g, 3.99 mmol, 1.1 equiv) in THF (3.6 mL) and the mixture was stirred at 25 °C for 4 h. The reaction mixture was then quenched with water (30 mL) and the aqueous layer extracted with DCM (3 x 30 mL), the combined organic layers dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude product was purified by FCC (10% EtOAc in cyclohexane) to obtain (*E*)-N,4-dimethyl-N-(6-phenylhex-3-en-1-yl)benzenesulfonamide (725 mg, 2.11 mmol, 58%) as a colourless oil.

Rf = 0.47 (10% EtOAc in Cy).

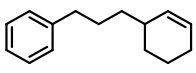
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.70 – 7.62 (m, 2H), 7.28 (m, 4H), 7.21 – 7.11 (m, 3H), 5.58 – 5.45 (m, 1H), 5.42 – 5.30 (m, 1H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.69 (s, 4H), 2.68 – 2.61 (m, 2H), 2.42 (s, 3H), 2.35 – 2.25 (m, 2H), 2.26 – 2.16 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 143.3, 142.0, 134.9, 132.4, 129.7, 128.6, 128.4, 127.5, 126.7, 125.9, 50.2, 35.9, 34.9, 34.5, 31.3, 21.6.

IR (neat): ν (cm^{-1}) 2927.7, 1599.0, 1454.8, 1340.5, 1260.6, 1089.8, 968.8,.

HRMS (ESI): Calcd for $C_{20}H_{25}NO_2SNa$ $[M+Na]^+$: 366.1498, found 366.1505.

(3-(Cyclohex-2-en-1-yl)propyl)benzene (**3.1q**)



1-Bromo-3-phenylpropane (1.5 mL, 9.99 mmol, 1.0 equiv) was added slowly to a suspension of magnesium turnings (267 mg, 11.0 mmol, 1.1 equiv) and a crystal of iodine in anhydrous Et_2O (6.7 mL). The reaction mixture was then heated under reflux for 4 h. The reaction mixture

was then cooled down to 25 °C and 3-bromocyclohexene (1.3 mL, 9.99 mmol, 1.0 equiv) was added to the reaction mixture. The reaction was heated under reflux for 4 h, and then quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer extracted with Et_2O (3 x 10 mL) and the combined organic layers dried over $MgSO_4$. The volatiles were removed under reduced pressure and the crude product purified by FCC (cyclohexane) to obtain (3-(cyclohex-2-en-1-yl)propyl)benzene (1.25 g, 6.24 mmol, 63%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[263]

Rf = 0.8 (cyclohexane).

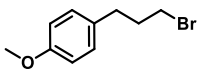
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 5.76 – 5.64 (m, 1H), 5.64 – 5.54 (m, 1H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.18 – 2.04 (m, 1H), 2.04 – 1.93 (m, 2H), 1.83 – 1.66 (m, 4H), 1.58 – 1.22 (m, 4H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.9, 132.2, 128.5, 128.4, 127.0, 125.7, 36.4, 36.2, 35.2, 29.2, 29.0, 25.5, 21.7.

IR (neat): ν (cm^{-1}) 3021.8, 2927.0, 2855.6, 1604.0, 1453.3, 745.8, 697.6.

HRMS (ESI): Calcd for $C_{15}H_{20}Ag$ $[M+Ag]^+$: 307.0610, found 307.0610.

1-(3-Bromopropyl)-4-methoxybenzene (**3.18d**)



PPh_3 (6.30 g, 24.0 mmol, 1.2 equiv) was added portionwise to a solution of 3-(4-methoxyphenyl)propan-1-ol (3.32 g, 20.0 mmol, 1.0 equiv) and CBr_4 (7.96 g, 24.0 mmol, 1.2 equiv) in DCM (40.0 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. The reaction mixture was then filtered over Celite® and the volatiles removed under reduced pressure. The crude product was purified by FCC (2.5 % Et_2O in cyclohexane) to obtain 1-(3-bromopropyl)-4-methoxybenzene (4.26 g, 18.6 mmol, 93%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[264]

Rf = 0.45 (2.5 % Et_2O in Cy).

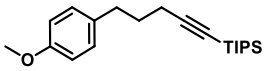
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.17 – 7.08 (m, 2H), 6.90 – 6.79 (m, 2H), 3.80 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.14 (tt, *J* = 7.3, 6.6 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.1, 132.7, 129.6, 114.0, 55.4, 34.5, 33.3, 33.1.

IR (neat): ν (cm^{-1}) 2934.7, 1612.0, 1511.3, 1460.5, 1241.4, 1177.4, 1034.9, 828.8.

HRMS (ESI): Calcd for $C_{10}H_{13}BrOAg$ $[M+Ag]^+$: 334.9195, found 334.9196.

Triisopropyl(5-(4-methoxyphenyl)pent-1-yn-1-yl)silane (**3.26**)



The title product was obtained following general procedure **H** from 1-(3-bromopropyl)-4-methoxybenzene (**3.18d**, 1.57 g, 6.86 mmol, 1.0 equiv), and (triisopropylsilyl)acetylen (2.0 mL, 8.92 mmol, 1.3 equiv). The crude product was purified by fractional distillation (158 °C, 0.03 mbar) to obtain triisopropyl(5-(4-methoxyphenyl)pent-1-yn-1-yl)silane (1.50 g, 6.54 mmol, 66%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[265]

Bp: 158 °C, 0.03 mbar.

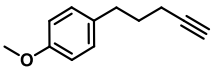
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.14 – 7.08 (m, 2H), 6.87 – 6.78 (m, 2H), 3.79 (s, 3H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 6.9 Hz, 2H), 1.80 (tt, *J* = 7.6, 6.9 Hz, 2H), 1.09 (s, 3H), 1.08 (s, 18H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.0, 134.0, 129.6, 113.9, 108.9, 80.8, 55.4, 33.9, 31.0, 19.37, 18.8, 11.5.

IR (neat): ν (cm^{-1}) 2940.1, 2863.7, 2170.1, 1612.5, 1512.1, 1462.4, 1299.9, 1244.9, 1038.3, 882.9, 660.4.

HRMS (ESI): Calcd for $C_{21}H_{34}OSiAg$ $[M+Ag]^+$: 437.1424, found 437.1427.

1-Methoxy-4-(pent-4-yn-1-yl)benzene (**3.27**)



Tetrabutylammonium fluoride (1.0 M, 6.8 mL, 6.81 mmol, 1.5 equiv) was added to a solution of triisopropyl(5-(4-methoxyphenyl)pent-1-yn-1-yl)silane (**3.26**, 1.50 g, 4.54 mmol, 1.0 equiv) and water (164 µL, 9.08 mmol, 2.0 equiv) in THF (18 mL) and the reaction mixture was stirred for 2 h. Sat. aq. $NaHCO_3$ (20 mL) was then added to the reaction mixture and the layers separated. The aqueous phase was extracted with Et_2O (3 x 30 mL), the combined organic layers dried over $MgSO_4$ and the volatiles removed under reduced pressure to obtain 1-methoxy-4-(pent-4-yn-1-yl)benzene (785 mg, 4.50 mmol, 99%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[266]

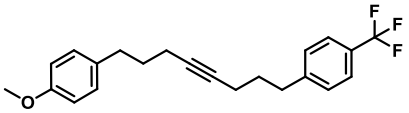
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.17 – 7.08 (m, 2H), 6.88 – 6.79 (m, 2H), 3.80 (s, 3H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.20 (td, *J* = 7.0, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.82 (tt, *J* = 7.6, 7.0 Hz, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.0, 133.7, 129.6, 113.9, 84.4, 68.7, 55.4, 33.8, 30.4, 17.9.

IR (neat): ν (cm^{-1}) 3296.3, 2935.2, 1612.0, 1511.8, 1460.7, 1243.4, 1177.6, 1036.6, 909.5, 732.1, 632.5.

HRMS (ESI): Calcd for $C_{12}H_{14}OAg$ $[M+Ag]^+$: 281.0090, found 281.0092.

1-Methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-yn-1-yl)benzene (**3.28**)



The title product was obtained following general procedure **H** from 1-(3-bromopropyl)-4-(trifluoromethyl)benzene (**3.19b**, 881 mg, 3.30 mmol, 1.1 equiv), and 1-methoxy-4-(pent-4-yn-1-yl)benzene (**3.27**, 523 mg, 3.00 mmol, 1.0 equiv). The crude product was purified by FCC (2% Et_2O in cyclohexane) to obtain 1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-yn-1-yl)benzene (680 mg, 1.89 mmol, 63%) as a colourless oil.

Rf = 0.3 (2% Et_2O in Cy).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.51 (m, 2H), 7.34 – 7.28 (m, 2H), 7.14 – 7.09 (m, 2H), 6.86 – 6.80 (m, 2H), 3.79 (s, 3H), 2.80 (t, *J* = 7.7 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.24 – 2.16 (m, 4H), 1.88 – 1.74 (m, 4H).

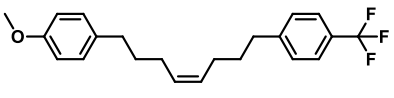
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 158.0, 146.1 (q, *J* = 1.4 Hz), 134.0, 129.5, 129.0, 128.4 (q, *J* = 32.3 Hz), 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.8 Hz), 113.9, 80.9, 79.9, 55.4, 34.7, 34.1, 31.1, 30.5, 18.3, 18.3.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.30.

IR (neat): ν (cm^{-1}) 2935.9, 1614.8, 1512.1, 1323.9, 1244.9, 1162.2, 1119.7, 1067.1, 1037.6, 836.7.

HRMS (ESI): Calcd for $C_{22}H_{23}F_3OAg$ $[M+Ag]^+$: 467.0746, found 467.0756.

(*Z*)-1-Methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl)benzene (**3.1r**)



The title compound was obtained following general procedure **I** from 1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-yn-1-yl)benzene (**3.28**, 338 mg, 0.938 mmol, 1.0 equiv). The crude product was purified by FCC (1% Et_2O in cyclohexane) to obtain (*Z*)-1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl)benzene (336 mg, 0.927mmol, 99%, *E*/*Z* = <1:99) as a colourless oil.

Rf = 0.2 (1% Et_2O in Cy).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.50 (m, 2H), 7.31 – 7.25 (m, 2H), 7.12 – 7.06 (m, 2H), 6.86 – 6.80 (m, 2H), 5.49 – 5.35 (m, 2H), 3.80 (s, 3H), 2.67 (t, *J* = 7.7 Hz, 2H), 2.56 (t, *J* = 7.8 Hz, 2H), 2.11 – 1.99 (m, 4H), 1.74 – 1.61 (m, 4H).

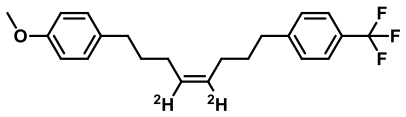
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 157.9, 146.8 (q, *J* = 1.6 Hz), 134.7, 130.4, 129.5, 129.4, 128.9, 128.2 (q, *J* = 32.2 Hz), 125.3 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 271.7 Hz), 113.8, 55.4, 35.4, 34.7, 31.8, 31.2, 26.9, 26.9.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.24.

IR (neat): ν (cm^{-1}) 2932.2, 2858.1, 1615.0, 1511.9, 1323.9, 1244.4, 1161.8, 1119.1, 1067.2, 1037.8, 909.3, 839.1, 733.1.

HRMS (ESI): Calcd for $C_{22}H_{25}F_3OAg$ $[M+Ag]^+$: 469.0903, found 469.0908.

(*Z*)-1-Methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl-4,5-d2)benzene (**3.1r-*D*$_2$**)



The title compound was obtained following general procedure **I** from 1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-yn-1-yl)benzene (**3.28**, 338 mg, 0.938 mmol, 1.0 equiv) and deuterium instead of hydrogen. The crude product was purified by FCC (1% Et_2O in cyclohexane) to obtain *(Z)*-1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl-4,5-d2)benzene (342 mg, 0.938mmol, quant., *E*/*Z* = <1:99) as a colourless oil.

Rf = 0.2 (1% Et_2O in Cy).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.59 – 7.50 (m, 2H), 7.32 – 7.25 (m, 2H), 7.15 – 7.07 (m, 2H), 6.90 – 6.80 (m, 2H), 3.80 (s, 3H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.13 – 1.99 (m, 4H), 1.75 – 1.60 (m, 4H).

^{2}H-NMR (77 MHz, $CDCl_3$): δ (ppm) 4.85 (bs, 2^{2}H).

^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 157.9, 146.8 (q, *J* = 1.4 Hz), 134.7, 129.9 (non-binomial t, *J* = 23.4, 22.2 Hz), 129.4, 129.0 (non-binomial t, *J* = 23.4, 22.2 Hz), 128.2 (q, *J* = 32.3 Hz), 125.3 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 271.7 Hz), 113.8, 55.4, 35.4, 34.7, 31.7, 31.2, 26.8, 26.7.

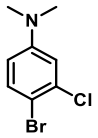
^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) 62.23.

IR (neat): ν (cm^{-1}) 2932.6, 2857.8, 1615.2, 1511.9, 1323.9, 1244.7, 1161.7, 1118.6, 1067.0, 1037.8, 830.5.

HRMS (ESI): Calcd for $C_{22}H_{23}D_2F_3OAg$ $[M+Ag]^+$: 471.1028, found 471.1032.

6.3.2. Synthesis of aryl-bromides

4-Bromo-3-chloro-N,N-dimethylaniline (**S1a**)

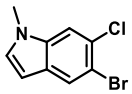


4-bromo-3-chloro-N,N-dimethylaniline was prepared according to an adapted reported procedure.[267] Sodium cyanoborohydride (960 mg, 14.5 mmol, 2.0 equiv) was added to a stirred slurry of 4-bromo-3-chloroaniline (1.50 g, 7.26 mmol, 1 equiv) and paraformaldehyde (1.34 g, 14.9 mmol, 2.05 equiv) in glacial acetic acid (10 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 25 min whereupon the ice bath was removed and the mixture was heated to 65 °C and stirred at that temperature for 3 h. The hot reaction mixture was poured over aq. NaOH (5 M, 39 mL, 193 mmol, 1.1 equiv to acetic acid) and then diluted with ethyl acetate (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed sequentially with water (20 mL) and Brine (20 mL), and then dried over $MgSO_4$. The dried solution was filtered and concentrated to afford 4-bromo-3-chloro-N,N-dimethylaniline (1.46 g, 7.26 mmol, 86%) as an off-white solid. Spectroscopic data are consistent with those previously reported.[267]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, *J* = 9.0 Hz, 1H), 6.76 (d, *J* = 3.0 Hz, 1H), 6.46 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.93 (s, 6H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ 150.5, 134.7, 133.6, 113.7, 112.3, 107.7, 40.5.

5-Bromo-6-chloro-1-methyl-1H-indole (**S1b**)



NaH (60% in mineral oil, 521 mg, 13.0 mmol, 3.0 equiv) was added to a solution of 5-bromo-6-chloro-1H-indole (1.00 g, 4.34 mmol, 1.0 equiv) in dry THF (25 mL). After 30 min, CH_3I (0.82 mL, 13.0 mmol, 3.0 equiv) was added dropwise to the reaction mixture and stirred at 25 °C for 14 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FCC (5% EtOAc in Cyclohexane) to obtain 5-bromo-6-chloro-1-methyl-1H-indole (797 mg, 3.26 mmol, 75%) as an off-white solid.

Rf = 0.4 (5% EtOAc in Cy).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (s, 1H), 7.42 (d, *J* = 0.9 Hz, 1H), 7.04 (d, *J* = 3.1 Hz, 1H), 6.40 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.73 (s, 3H).

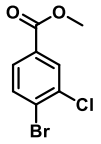
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 136.3, 130.8, 128.7, 127.0, 125.1, 112.7, 110.8, 100.7, 33.2.

IR (neat): ν (cm^{-1}) 3100.3, 2939.0, 1508.4, 1473.7, 1426.1, 1313.8, 1262.9, 1088.6, 927.0, 877.8.

MP: 108.6 °C.

HRMS (ESI): Calcd for C $C_9H_7BrClNAg$ ($[M+Ag]^+$) 351.8477, found 351.8479.

Methyl 4-bromo-3-chlorobenzoate (**S1c**)



A drop of conc. sulfuric acid was added to a solution of 4-bromo-3-chlorobenzoic acid (4.99 g, 21.2 mmol, 1.0 equiv) in MeOH (20 mL, 494 mmol, 23.3 equiv) and the reaction mixture was stirred at 50 °C for 1 h. The volatiles were removed under reduced pressure and methyl 4-bromo-3-chlorobenzoate (4.74 g, 19.0 mmol, 90%) was obtained as an off-white solid. Spectroscopic data are consistent with those previously reported.[239]

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.3, 2.0 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 3.92 (s, 3H).

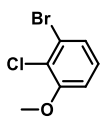
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 165.5, 135.1, 134.0, 131.4, 130.8, 128.8, 128.2, 52.7.

IR (neat): ν (cm^{-1}) 2953.0, 1728.5, 1588.6, 1435.0, 1376.7, 1287.8, 1240.0, 1104.7, 1021.7, 757.7.

MP: 62.7 °C.

HRMS (ESI): Calcd for $C_8H_6BrClO_2Na$ $[M+Na]^+$: 270.9132, found 270.9128

1-Bromo-2-chloro-3-methoxybenzene (**S1d**)



CH_3I (0.53 mL, 8.52 mmol, 2.0 equiv) was added to a mixture of 3-bromo-2-chlorophenol (884 mg, 4.26 mmol, 1.0 equiv) and K_2CO_3 (1.18 g, 8.52 mmol, 2.0 equiv) in DMF (4.4 mL) and the reaction mixture was stirred for 14 h at 50 °C. The reaction mixture was allowed to cool down

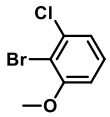
to 25 °C and diluted with Et_2O (50 mL). The organic layer was washed with a 1:1 mixture of water and Brine (5 x 30 mL), dried over $MgSO_4$ and the concentrated *in vacuo*. The crude product was purified by FCC (2.5% Et_2O in PET) to obtain 1-bromo-2-chloro-3-methoxybenzene (920 mg, 4.15 mmol, 98%) as a colourless oil. Spectroscopic data are consistent with those previously reported.[268]

Rf = 0.4 (2.5% Et_2O in PET).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 8.3, 1.4 Hz, 1H), 3.90 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 156.5, 128.0, 125.5, 124.0, 123.5, 110.7, 56.6.

2-Bromo-1-chloro-3-methoxybenzene (**S1e**)



CH_3I (0.56 mL, 9.06 mmol, 2.0 equiv) was added to a mixture of 2-bromo-3-chlorophenol (940 mg, 4.53 mmol, 1.0 equiv) and K_2CO_3 (1.25 g, 9.06 mmol, 2.0 equiv) in DMF (4.7 mL) and the reaction mixture was stirred for 14 h at 50 °C. The reaction mixture was allowed to cool down to 25 °C and diluted with Et_2O (50 mL). The organic layer was washed with a 1/1 mixture of water and Brine (5 x 30 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The crude product was purified by FCC (2.5% Et_2O in PET) to obtain 2-bromo-1-chloro-3-methoxybenzene (993 mg, 4.49 mmol, 99%) as a colourless oil.

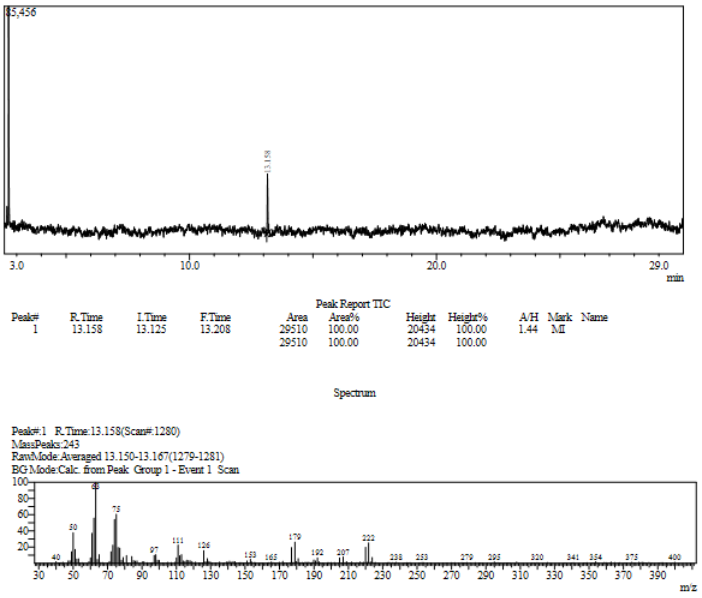
Rf = 0.4 (2.5% Et_2O in PET).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.79 (dd, *J* = 8.3, 1.4 Hz, 1H), 3.91 (s, 3H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 157.6, 136.0, 128.5, 122.5, 112.8, 109.9, 56.8.

IR (neat): ν (cm^{-1}) 2939.9, 1577.7, 1461.8, 1267.5, 1052.7, 767.8, 670.0.

GCMS (EI): main fragment peak: (m/z) 222.



6.3.3. Palladium catalysed migratory arylation of alkenes

General Procedure **J**: One-Pot Hydroboration – Migratory Suzuki-Miyaura Coupling

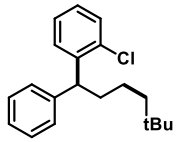
The olefin (0.600 mmol, 1.2 equiv) was charged in an oven-dried 10 mL catalysis tube equipped with a stirring bar and septum, and then purged and filled with Argon three times. A borane dimethyl sulfide complex solution in toluene (2 M, 0.35 mL, 0.700 mmol, 1.4 equiv) was then added and the tube placed in a metal heating block set at 60 °C with stirring, fitted with a balloon. After 1 h water (0.10 mL, 5.55 mmol, 11.1 equiv) was added to the reaction mixture, which was further stirred at 60 °C for 1 h. The balloon was then swapped with a line from the Schlenk and the volatiles were removed under high vacuum at 60 °C for 1 h. After allowing the tube cool down to 25 °C it was transferred in a glovebox and $Pd(TFA)_2$ (8.31 mg, 0.025 mmol, 5 mol%), $(t\text{Bu})_2\text{PMe}\bullet\text{HBF}_4$ (18.6 mg, 0.075 mmol, 15 mol%), Cs_2CO_3 (489 mg, 1.50 mmol, 3.0 equiv) and aryl bromide (0.500 mmol, 1.0 equiv) (if solid) were charged in the catalysis tube. Outside of the glovebox, toluene (1.0 mL), water (0.2 mL) and the aryl bromide (0.500 mmol, 1.0 equiv) (if liquid) were added. The septum was rapidly exchanged for a screw cap, the catalysis tube sealed with Teflon-tape and then placed in a heating block set at 120 °C with vigorous stirring for 48 h. After this period the reaction mixture was allowed to cool to 25 °C and filtered over Celite® with EtOAc. The volatiles were removed under reduced pressure and the crude product was analyzed with GC-MS to determine the regioselectivity and then purified by FCC to yield the corresponding 1,1-diarylalkanes.

General Procedure **K**: Large Scale One-Pot Hydroboration – Migratory Suzuki-Miyaura Coupling without a glovebox.

The olefin (6.00 mmol, 1.2 equiv) was charged in two-neck flask equipped with a condenser, a Schlenk-bubbler, a stirring bar and a septum and then purged and filled with Argon three times. A borane dimethyl sulfide complex solution in toluene (2 M, 3.5 mL, 7.00 mmol, 1.4 equiv) was then added and the reaction mixture was stirred at 60 °C for 1 h. After 1 h water

(1.0 mL, 55.5 mmol, 11.1 equiv) was added to the reaction mixture, which was further stirred at 60 °C for 1 h. The volatiles were then carefully removed under high vacuum through the Schlenk-Bubbler at 60 °C for 1 h. The septum of the two-neck flask was removed under a flow of Argon after allowing the flask to cool down to 25 °C. $Pd(TFA)_2$ (83.1 mg, 0.250 mmol, 5 mol%), $(t\text{Bu})_2\text{PMe}\bullet\text{HBF}_4$ (186 mg, 0.750 mmol, 15 mol%), Cs_2CO_3 (4.89 g, 1.50 mmol, 3.0 equiv), aryl bromide (5.00 mmol, 1.0 equiv), toluene (10 mL) and water (2.0 mL) were added and open neck closed with a glass-lid. The reaction mixture was then heated to 120 °C under vigorous stirring for 48 h. After this period the reaction mixture was allowed to cool to 25 °C and filtered over Celite® with EtOAc. The volatiles were removed under reduced pressure and the crude product was analyzed with GC-MS to determine the regioselectivity and then purified by FCC to yield the corresponding 1,1-diarylalkanes.

1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**)



The title compound was obtained following general procedure **J** from (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**, 144 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (150 mg, 0.500 mmol, quant.) as a colourless oil.

Large scale and without a Glovebox: The title compound was obtained in a ten-fold bigger scale (5.00 mmol) following general procedure **K** from (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**, 1.13 g, 6.00 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (0.58 mL, 5.00 mmol, 1.0 equiv) to obtain 1-chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (1.37 g, 4.54 mmol, 91%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.84 (cyclohexane).

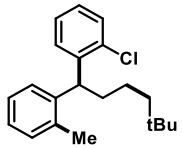
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 – 7.26 (m, 5H), 7.26 – 7.14 (m, 3H), 7.14 – 7.06 (m, 1H), 4.50 (t, *J* = 7.7 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.29 – 1.18 (m, 4H), 0.82 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 144.0, 142.7, 134.4, 129.8, 128.6, 128.4, 128.3, 127.3, 127.0, 126.3, 46.8, 44.2, 36.5, 30.5, 29.5, 22.9.

IR (neat): ν (cm^{-1}) 3027.1, 2951.6, 1600.4, 1470.2, 1364.2, 1249.4, 907.4, 731.0, 670.0.

HRMS (ESI): Calcd for $C_{20}H_{26}Ag$ $[M+Ag]^+$: 373.1080, found 373.1079.

1-Chloro-2-(5,5-dimethyl-1-(o-tolyl)hexyl)benzene (**3.3c**)



The title compound was obtained following general procedure **J** from (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-2-methylbenzene (**3.1d**, 121 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(5,5-dimethyl-1-(o-tolyl)hexyl)benzene (101 mg, 0.320 mmol, 64%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.48 (cyclohexane).

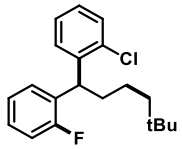
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 – 7.30 (m, 1H), 7.27 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H), 7.15 – 7.04 (m, 5H), 4.58 (t, *J* = 7.5 Hz, 1H), 2.24 (s, 3H), 1.95 – 1.86 (m, 2H), 1.39 – 1.19 (m, 4H), 0.81 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 142.6, 141.8, 137.1, 134.4, 130.7, 129.6, 129.1, 127.2, 126.9, 126.9, 126.3, 125.9, 44.4, 43.2, 36.6, 30.5, 29.5, 23.1, 19.8.

IR (neat): ν (cm^{-1}) 3949.8, 1468.5, 1364.2, 1249.3, 122.7, 1035.2, 909.0, 747.3, 686.7.

HRMS (ESI): Calcd for $C_{21}H_{27}ClAg$ $[M+Ag]^+$: 421.0847, found 421.0845.

1-Chloro-2-(1-(2-fluorophenyl)-5,5-dimethylhexyl)benzene (**3.3d**)



The title compound was obtained following general procedure **J** from (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-2-fluorobenzene (**3.1e**, 124 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(1-(2-fluorophenyl)-5,5-dimethylhexyl)benzene (115 mg, 0.360 mmol, 72%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.48 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 1H NMR (500 MHz, CDCl3) δ 7.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.21 (td, *J* = 7.6, 1.4 Hz, 1H), 7.18 – 7.09 (m, 3H), 7.07 – 7.02 (m,

1H), 7.02 – 6.95 (m, 1H), 4.75 (t, *J* = 7.7 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.30 – 1.17 (m, 4H), 0.81 (s, 9H).

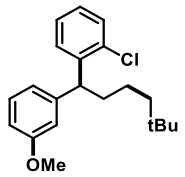
$^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ (ppm) 161.2 (d, *J* = 246.1 Hz), 141.5, 134.6, 130.9 (d, *J* = 14.6 Hz), 129.8, 129.2 (d, *J* = 4.6 Hz), 128.8 (d, *J* = 1.3 Hz), 127.9 (d, *J* = 8.3 Hz), 127.6, 126.8, 124.0 (d, *J* = 3.5 Hz), 115.5 (d, *J* = 22.8 Hz), 44.2, 40.2 (d, *J* = 2.0 Hz), 35.8, 30.5, 29.5, 27.1, 22.8.

$^{19}F\{^{1}H\}$-NMR (470 MHz, $CDCl_3$): δ (ppm) -116.63.

IR (neat): ν (cm^{-1}) 3065.9, 2951.2, 1586.1, 1472.0, 1364.4, 1228.1, 1095.1, 1037.1, 908.0, 749.6.

HRMS (ESI): Calcd for $C_{20}H_{24}ClFAg$ $[M+Ag]^+$: 425.0596, found 425.0591.

1-Chloro-2-(1-(3-methoxyphenyl)-5,5-dimethylhexyl)benzene (**3.3e**)



The title compound was obtained following general procedure **J** from (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-3-methoxybenzene (**3.1f**, 131 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(1-(3-methoxyphenyl)-5,5-dimethylhexyl)benzene (105 mg, 0.318 mmol, 64%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.3 (2% Et_2O in Cy).

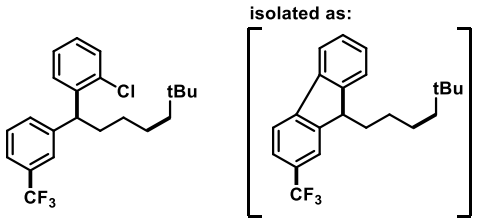
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (td, *J* = 7.9, 1.6 Hz, 2H), 7.23 – 7.14 (m, 2H), 7.08 (td, *J* = 7.6, 1.7 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.81 (bs, 1H), 6.71 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.47 (t, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 2.03 – 1.91 (m, 2H), 1.27 – 1.17 (m, 4H), 0.81 (s, 9H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 159.7, 145.7, 142.6, 134.4, 129.7, 129.3, 128.6, 127.3, 127.0, 120.8, 114.5, 111.1, 55.2, 46.7, 44.2, 36.5, 30.5, 29.5, 22.9.

IR (neat): ν (cm^{-1}) 2951.3, 1599.2, 1469.5, 1255.9, 1153.4, 1047.7, 906.3, 728.0, 649.3.

HRMS (ESI): Calcd for $C_{21}H_{27}ClOAg$ $[M+Ag]^+$: 437.0796, found 437.0790.

9-(5,5-Dimethylhexyl)-2-(trifluoromethyl)-9H-fluorene (**3.25a**)



The title compound was obtained following general procedure **J** from (*Z*)-1-(6,6-dimethylhept-4-en-1-yl)-3-(trifluoromethyl)benzene (**3.1g**, 162 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(6,6-dimethyl-1-(3-(trifluoromethyl)phenyl)heptyl)benzene (**3g**) as a colourless oil. The crude product was further engaged in a cyclization reaction due to impossible separation from the cyclized side product as follows.[25] 1-chloro-2-(6,6-dimethyl-1-(3-(trifluoromethyl)phenyl)heptyl)benzene (**3g** ,191 mg, 0.500 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.37 mg, 0.015 mmol, 3 mol%), PCy_3 (8.41 mg, 0.030 mmol 6 mol%) and CsOPiv(351 mg, 1.50 mmol, 3.0 equiv) were charged in a vial, which was purged and filled with Argon three times. THF (2.0 mL) was added and the septum exchanged with a cap. The vial was then placed in a heating block set at 120 °C with vigorous stirring for 12 h. The reaction mixture was then filtered over Celite® and the volatiles removed under reduced pressure. The crude product was then purified by FCC (cyclohexane) to obtain 9-(5,5-dimethylhexyl)-2-(trifluoromethyl)-9H-fluorene (141 mg, 0.407 mmol, 81% over the two steps).

rr: (benzylic vs. others) >99:1.

Rf = 0.65 (cyclohexane).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.85 – 7.78 (m, 2H), 7.78 – 7.74 (m, 1H), 7.66 – 7.62 (m, 1H), 7.59 – 7.54 (m, 1H), 7.43 – 7.38 (m, 2H), 4.04 (t, *J* = 5.9 Hz, 1H), 2.11 – 1.99 (m, 2H), 1.24 – 1.12 (m, 4H), 1.12 – 1.07 (m, 2H), 0.83 (s, 9H).

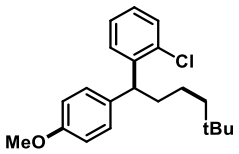
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 148.4, 148.1, 144.7 (q, *J* = 1.4 Hz), 139.8, 128.8 (q, *J* = 31.8 Hz), 128.1, 127.3, 124.9 (q, *J* = 271.9 Hz), 124.7, 124.4 (q, *J* = 3.9 Hz), 121.3 (q, *J* = 3.8 Hz), 120.7, 120.0, 47.8, 44.1, 33.0, 30.4, 29.5, 26.7, 25.0.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) -61.58.

IR (neat): ν (cm^{-1}) 2934.3, 1620.6, 1426.5, 1325.7, 1161.2, 1118.3, 1064.4, 895.8, 834.3, 734.8.

HRMS (ESI): Calcd for $C_{22}H_{25}F_3Ag$ $[M+Ag]^+$: 453.0954, found 453.0947.

1-Chloro-2-(1-(4-methoxyphenyl)-5,5-dimethylhexyl)benzene (**3.3g**)



The title compound was obtained following general procedure **J** from (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-4-methoxybenzene (**3.1h**, 131 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(1-(4-methoxyphenyl)-5,5-dimethylhexyl)benzene (117 mg, 0.354 mmol, 71%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.3 (2% Et_2O in Cy).

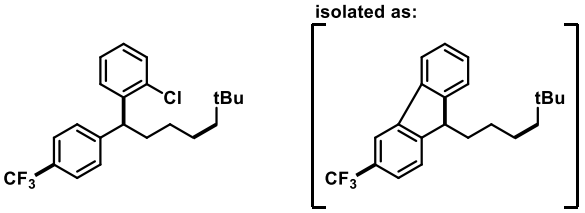
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.28 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.21 (ddd, *J* = 7.5, 1.3 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.10 (ddd, *J* = 7.5, 1.7 Hz, 1H), 6.86 – 6.79 (m, 2H), 4.43 (t, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 1.99 – 1.90 (m, 2H), 1.29 – 1.20 (m, 4H), 0.81 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.0, 143.1, 136.1, 134.3, 129.8, 129.2, 128.5, 127.2, 127.0, 113.8, 55.3, 45.9, 44.2, 36.7, 30.5, 29.5, 22.9.

IR (neat): ν (cm^{-1}) 2949.8, 1610.4, 1511.0, 1468.4, 1364.0, 1247.2, 1177.9, 1036.9, 908.3, 825.0.

HRMS (ESI): Calcd for $C_{21}H_{27}ClOAg$ $[M+Ag]^+$: 437.0796, found 437.0794.

9-(5,5-Dimethylhexyl)-3-(trifluoromethyl)-9H-fluorene (**3.25b**)



The title compound was obtained following general procedure **J** from (*Z*)-1-(6,6-dimethylhept-4-en-1-yl)-4-(trifluoromethyl)benzene (**3.1i**, 162 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(6,6-dimethyl-1-(4-(trifluoromethyl)phenyl)heptyl)benzene (**3i**) as a colourless oil. The crude product was further engaged in a cyclization reaction due to impossible separation from the cyclized side product as follows.[25] 1-chloro-2-(6,6-dimethyl-1-(4-(trifluoromethyl)phenyl)heptyl)benzene (**3i**, 191 mg, 0.500 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.37 mg, 0.015 mmol, 3 mol%), PCy_3 (8.41 mg, 0.030 mmol 6 mol%) and CsOPiv (351 mg, 1.50 mmol, 3.0 equiv) were charged in a vial, which was purged and filled with Argon three times. THF (2.0 mL) was added and the septum exchanged with a cap. The vial was then placed in a heating block set at 120 °C with vigorous stirring for

12 h. The reaction mixture was then filtered over Celite® and the volatiles removed under reduced pressure. The crude product was then purified by FCC (cyclohexane) to obtain 9-(5,5-dimethylhexyl)-3-(trifluoromethyl)-9H-fluorene (135 mg, 0.390 mmol, 80% over the two steps).

rr: (benzylic vs. others) >99:1.

Rf = 0.65 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (bs, 1H), 7.86 – 7.78 (m, 1H), 7.66 – 7.54 (m, 3H), 7.45 – 7.35 (m, 2H), 4.04 (t, *J* = 5.9 Hz, 1H), 2.07 (dt, *J* = 9.8, 5.9 Hz, 2H), 1.28 – 1.20 (m, 2H), 1.20 – 1.09 (m, 4H), 0.86 (s, 9H).

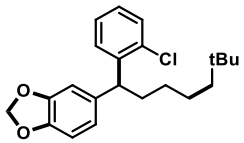
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 151.4 (q, *J* = 1.4 Hz), 147.8, 142.0, 139.9, 129.6 (q, *J* = 31.9 Hz), 127.9, 127.3, 124.8 (q, *J* = 272.2 Hz), 124.7, 124.6, 123.7 (q, *J* = 3.8 Hz), 120.3, 116.8 (q, *J* = 3.8 Hz), 47.8, 44.1, 33.0, 30.4, 29.5, 26.6, 25.0.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) -61.81.

IR (neat): ν (cm^{-1}) 2934.3, 1427.3, 1322.4, 1265.8, 1120.4, 1061.8, 892.7, 830.5, 737.3, 664.9.

HRMS (ESI): Calcd for $C_{22}H_{25}F_3Ag$ $[M+Ag]^+$: 453.0954, found 453.0948.

5-(1-(2-Chlorophenyl)-6,6-dimethylheptyl)benzo-1,3-dioxole (**3.3i**)



The title compound was obtained following general procedure **J** from (*Z*)-5-(6,6-Dimethylhept-4-en-1-yl)benzo-1,3-dioxole (**3.1j**, 148 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 5-(1-(2-chlorophenyl)-6,6-dimethylheptyl)benzo-1,3-dioxole (159 mg, 0.443 mmol, 89%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.32 (5% toluene in Cy).

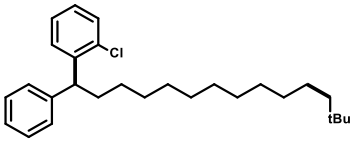
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.23 (td, *J* = 7.5, 1.4 Hz, 1H), 7.12 (td, *J* = 7.6, 1.7 Hz, 1H), 6.78 – 6.72 (m, 3H), 5.91 (d, *J* = 1.7 Hz, 2H), 4.40 (t, *J* = 7.7 Hz, 1H), 2.05 – 1.91 (m, 2H), 1.30 – 1.25 (m, 4H), 1.17 – 1.11 (m, 2H), 0.86 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.7, 145.9, 142.8, 138.0, 134.3, 129.8, 128.4, 127.3, 127.0, 121.3, 108.7, 108.2, 101.0, 46.5, 44.1, 35.8, 30.4, 29.5, 28.8, 24.6.

IR (neat): ν (cm^{-1}) 2932.9, 1486.1, 1363.7, 1240.8, 1119.6, 1039.6, 907.3, 806.8, 730.5, 647.8.

HRMS (ESI): Calcd for $C_{16}H_{23}O_2Ag$ $[M+Ag]^+$: 354.0743, found 354.0744.

1-Chloro-2-(13,13-dimethyl-1-phenyltetradecyl)benzene (**3.3j**)



The title compound was obtained following general procedure **J** from (*Z*)-(13,13-dimethyltetradec-11-en-1-yl)benzene (**3.1k**, 180 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(13,13-dimethyl-1-phenyltetradecyl)benzene (159 mg, 0385 mmol, 77%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

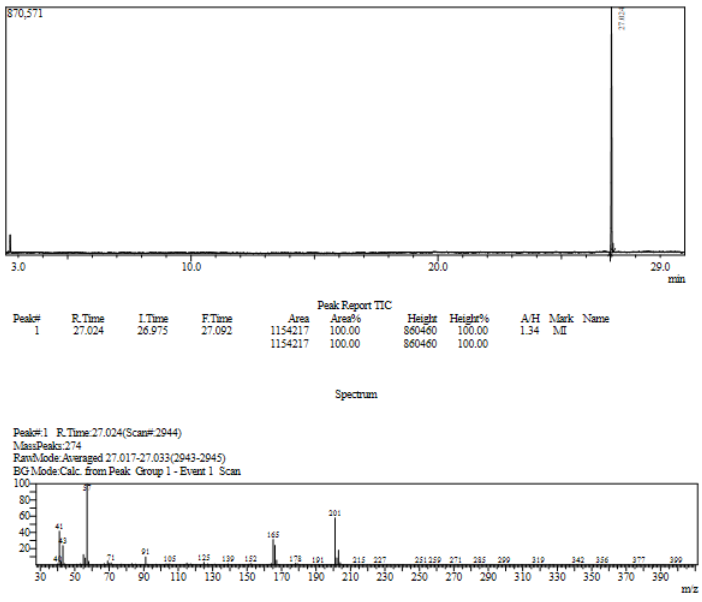
Rf = 0.7 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 – 7.29 (m, 2H), 7.26 (h, *J* = 2.5 Hz, 4H), 7.24 – 7.14 (m, 2H), 7.10 (td, *J* = 7.6, 1.7 Hz, 1H), 4.47 (t, *J* = 7.7 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.31 – 1.18 (m, 18H), 1.18 – 1.10 (m, 2H), 0.86 (s, 9H).

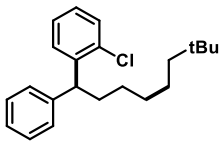
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 144.0, 142.8, 134.4, 129.8, 128.6, 128.4, 128.3, 127.3, 127.0, 126.3, 46.8, 44.4, 35.6, 30.8, 30.4, 29.9, 29.8, 29.8, 29.8, 29.8, 29.6, 29.6, 27.9, 24.7.

IR (neat): ν (cm^{-1}) 2925.8, 2854.2, 1468.4, 1363.3, 1036.0, 907.5, 732.6.

GCMS (EI): main fragment peaks: (m/z) 201, 165, 57.



1-Chloro-2-(7,7-dimethyl-1-phenyloctyl)benzene (**3.3k**)



The title compound was obtained following general procedure **J** from (*Z*)-(7,7-dimethyloct-4-en-1-yl)benzene (**3.1c**, 130 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(7,7-dimethyl-1-phenyloctyl)benzene (115 mg, 0.350 mmol, 70%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.78 (cyclohexane).

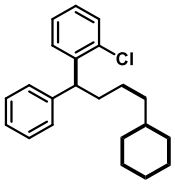
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.29 – 7.24 (m, 4H), 7.23 – 7.14 (m, 2H), 7.09 (dd, *J* = 7.8, 1.7 Hz, 1H), 4.48 (t, *J* = 7.7 Hz, 1H), 2.05 – 1.97 (m, 2H), 1.34 – 1.25 (m, 4H), 1.26 – 1.16 (m, 2H), 1.16 – 1.08 (m, 2H), 0.84 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 144.0, 142.8, 134.4, 129.8, 128.7, 128.5, 128.4, 127.3, 127.0, 126.3, 46.9, 44.4, 35.7, 30.7, 30.4, 29.6, 28.0, 24.6.

IR (neat): ν (cm^{-1}) 2932.2, 1470.5, 1036.7, 906.7, 729.7.

HRMS (ESI): Calcd for $C_{22}H_{29}ClAg$ $[M+Ag]^+$: 435.1003, found 435.0997.

1-Chloro-2-(4-cyclohexyl-1-phenylbutyl)benzene (**3.3l**)



The title compound was obtained following general procedure **J** from (*Z*)-(4-cyclohexylbut-3-en-1-yl)benzene (**3.1m**, 129 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(4-cyclohexyl-1-phenylbutyl)benzene (97 mg, 0.296 mmol, 59%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.5 (cyclohexane).

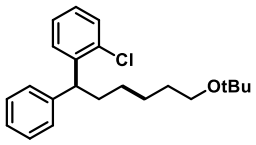
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 – 7.28 (m, 2H), 7.28 – 7.23 (m, 4H), 7.21 – 7.15 (m, 2H), 7.09 (td, *J* = 7.6, 1.7 Hz, 1H), 4.48 (t, *J* = 7.7 Hz, 1H), 2.03 – 1.97 (m, 2H), 1.65 – 1.58 (m, 4H), 1.35 – 1.07 (m, 9H), 0.88 – 0.76 (m, 2H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 144.0, 142.8, 134.4, 129.8, 128.6, 128.4, 128.3, 127.3, 127.0, 126.3, 46.8, 37.6, 35.9, 33.5, 33.5, 26.9, 26.5, 25.2.

IR (neat): ν (cm^{-1}) 2923.1, 2851.3, 1446.9, 1260.3, 1036.5, 906.3, 728.5.

HRMS (ESI): Calcd for $C_{22}H_{27}ClAg$ $[M+Ag]^+$: 433.0847, found 433.0842.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chlorobenzene (**3.3b**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-chlorobenzene (148 mg, 0.429 mmol, 86%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.45 (2% Et_2O in Cy).

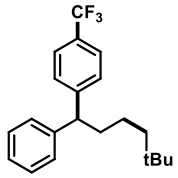
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.28 – 7.23 (m, 4H), 7.23 – 7.15 (m, 2H), 7.10 (td, *J* = 7.6, 1.8 Hz, 1H), 4.47 (t, *J* = 7.7 Hz, 1H), 3.29 (t, *J* = 6.5 Hz, 2H), 2.09 – 1.98 (m, 2H), 1.54 – 1.45 (m, 2H), 1.41 – 1.29 (m, 4H), 1.16 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 143.9, 142.7, 134.4, 129.7, 128.6, 128.4, 128.3, 127.30, 127.0, 126.3, 72.5, 61.6, 46.7, 35.6, 30.6, 27.7, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2930.9, 2859.6, 1601.9, 1469.5, 1361.4, 1197.4, 1083.2, 1035.1, 748.7, 698.3

HRMS (ESI): Calcd for $C_{22}H_{29}ClOAg$ $[M+Ag]^+$: 451.0952, found 451.0950.

1-(5,5-Dimethyl-1-phenylhexyl)-4-(trifluoromethyl)benzene (**3.3m**)



The title compound was obtained following general procedure **J** from (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**, 144 mg, 0.600 mmol, 1.2 equiv) and 4-Bromobenzotrifluoride (70 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(5,5-dimethyl-1-phenylhexyl)-4-(trifluoromethyl)benzene (163 mg, 0.0.487 mmol, 98%) as a colourless oil.

rr: (benzylic vs. others) 97:3.

Rf = 0.78 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 – 7.48 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.25 (m, 2H), 7.23 – 7.15 (m, 3H), 3.97 (t, *J* = 7.8 Hz, 1H), 2.10 – 1.94 (m, 2H), 1.26 – 1.17 (m, 4H), 0.80 (s, 9H).

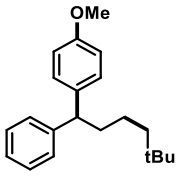
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 149.6 (q, *J* = 1.4 Hz), 144.4, 128.7, 128.5 (q, *J* = 32.1 Hz), 128.3, 128.0, 126.6, 125.5 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.8 Hz), 51.3, 44.2, 36.6, 30.5, 29.5, 23.0.

^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ (ppm) -62.27.

IR (neat): ν (cm^{-1}) 3028.7, 2951.2, 1619.2, 1323.7, 1122.0, 1068.4, 1018.2, 829.7, 740.5, 698.8.

HRMS (ESI): Calcd for $C_{21}H_{25}F_3Ag$ $[M+Ag]^+$: 441.0954, found 441.0948.

1-(5,5-Dimethyl-1-phenylhexyl)-4-methoxybenzene (**3.3n**)



The title compound was obtained following general procedure **J** from (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (1c, 144 mg, 0.600 mmol, 1.2 equiv) and 4-bromoanisole (63 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(5,5-dimethyl-1-phenylhexyl)-4-methoxybenzene (117 mg, 0.395 mmol, 79%) as a colourless oil.

rr: (benzylic vs. others) 92:8.

Rf = 0.3 (cyclohexane).

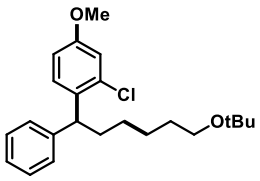
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25 – 7.12 (m, 7H), 6.83 – 6.75 (m, 2H), 3.85 (t, *J* = 7.8 Hz, 1H), 3.73 (s, 3H), 2.03 – 1.90 (m, 2H), 1.24 – 1.16 (m, 4H), 0.80 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 157.9, 145.9, 137.7, 128.9, 128.5, 127.9, 126.0, 113.9, 55.3, 50.5, 44.3, 37.0, 30.5, 29.5, 23.0.

IR (neat): ν (cm^{-1}) 2950.4, 1714.7, 1609.9, 1510.8, 1646.3, 1363.8, 1246.4, 1177.5, 1037.0, 910.0, 825.0, 731.4, 698.3.

HRMS (ESI): Calcd for $C_{21}H_{28}OAg$ $[M+Ag]^+$: 40.1186, found, 403.1180.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-4-methoxybenzene (**3.3o**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chloro-4-methoxybenzene (79 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-chloro-4-methoxybenzene (117 mg, 0.312 mmol, 62%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.14 (3% Et_2O in Cy).

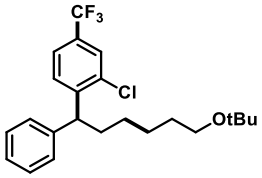
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.20 (m, 4H), 7.21 – 7.13 (m, 2H), 6.88 (d, *J* = 2.7 Hz, 1H), 6.76 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.38 (t, *J* = 7.7 Hz, 1H), 3.73 (s, 3H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.05 – 1.94 (m, 2H), 1.54 – 1.44 (m, 2H), 1.40 – 1.27 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.2, 144.4, 134.7, 134.7, 129.0, 128.4, 128.1, 126.1, 114.8, 113.3, 72.5, 61.6, 55.5, 46.0, 35.7, 30.6, 27.7, 27.7, 26.3.

IR (neat): ν (cm^{-1}) 2935.1, 1605.6, 1493.2, 1362.6, 1233.2, 1195.7, 1079.7, 1041.7, 907.2, 728.5, 648.4.

HRMS (ESI): Calcd for $C_{23}H_{31}ClO_2Ag$ $[M+Ag]^+$: 483.1052, found 483.1054.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-4-(trifluoromethyl)benzene (**3.3p**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chloro-4-(trifluoromethyl)benzene (74 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-chloro-4-(trifluoromethyl)benzene (124 mg, 0.300 mmol, 60%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.45 (2% Et_2O in Cy).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.62 – 7.58 (m, 1H), 7.48 – 7.42 (m, 1H), 7.42 – 7.38 (m, 1H), 7.31 – 7.17 (m, 5H), 4.50 (t, *J* = 7.7 Hz, 1H), 3.28 (t, *J* = 6.5 Hz, 2H), 2.12 – 1.93 (m, 2H), 1.54 – 1.44 (m, 2H), 1.40 – 1.25 (m, 4H), 1.15 (s, 9H).

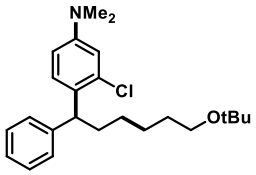
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ (ppm) 146.9 (q, *J* = 1.3 Hz), 142.8, 134.8, 129.7 (q, *J* = 33.1 Hz), 129.1, 128.7, 128.3, 126.8 (q, *J* = 3.9 Hz), 126.7, 123.8 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.3 Hz), 72.5, 61.5, 46.8, 35.4, 30.5, 27.7, 27.6, 26.3.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) -62.62.

IR (neat): ν (cm^{-1}) 2938.9, 1454.4, 1324.7, 1134.8, 1081.1, 907.7, 734.7, 651.3.

HRMS (ESI): Calcd for $C_{23}H_{28}ClF_3ONa$ $[M+Na]^+$: 435.1673, found 435.1676.

4-(6-(*tert*-Butoxy)-1-phenylhexyl)-3-chloro-N,N-dimethylaniline (**3.3q**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 4-bromo-3-chloro-N,N-dimethylaniline (**S1a**, 117 mg, 0.500 mmol, 1.0 equiv) to obtain 4-(6-(*tert*-butoxy)-1-phenylhexyl)-3-chloro-N,N-dimethylaniline (75.0 mg, 0.194 mmol, 39%) as a slightly yellow oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.2 (2.5% EtOAc in Cy).

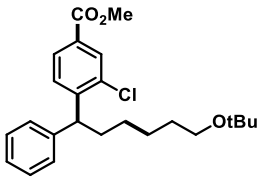
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29 – 7.18 (m, 4H), 7.18 – 7.08 (m, 2H), 6.67 (d, *J* = 2.7 Hz, 1H), 6.58 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.34 (t, *J* = 7.8 Hz, 1H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.88 (s, 6H), 2.05 – 1.93 (m, 2H), 1.54 – 1.43 (m, 2H), 1.41 – 1.26 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 149.6, 145.1, 134.9, 130.0, 128.7, 128.3, 128.1, 125.9, 113.2, 111.5, 72.5, 61.6, 45.9, 40.5, 35.7, 30.6, 27.8, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2933.9, 1609.5, 1507.7, 1444.8, 1360.7, 1197.3, 1078.7, 962.8, 906.9, 728.0, 648.2.

HRMS (ESI): Calcd for $C_{24}H_{34}ClNOH$ $[M+H]^+$: 388.2402, found 388.2403.

Methyl 4-(6-(*tert*-butoxy)-1-phenylhexyl)-3-chlorobenzoate (**3.3r**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and methyl 4-bromo-3-chlorobenzoate (**S1c**, 125 mg, 0.500 mmol, 1.0 equiv) to obtain methyl 4-(6-(*tert*-butoxy)-1-phenylhexyl)-3-chlorobenzoate (72.0 mg, 0.179 mmol, 36%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.35 (5% EtOAc in Cy).

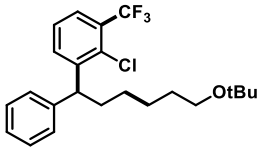
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (d, J = 1.8 Hz, 1H), 7.86 (dd, J = 8.2, 1.8 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.29 – 7.21 (m, 4H), 7.20 – 7.15 (m, 1H), 4.50 (t, J = 7.7 Hz, 1H), 3.89 (s, 3H), 3.28 (t, J = 6.5 Hz, 2H), 2.03 (td, J = 7.7, 2.5 Hz, 2H), 1.51 – 1.48 (m, 2H), 1.42 – 1.35 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 166.0, 147.9, 143.0, 134.6, 130.9, 129.4, 128.6, 128.6, 128.3, 128.1, 126.6, 72.5, 61.5, 52.4, 47.0, 35.4, 30.5, 27.7, 27.7, 26.3.

IR (neat): ν (cm^{-1}) 2934.5, 1724.2, 1453.9, 1391.8, 1256.4, 1195.6, 1117.0, 978.1, 908.6, 729.2, 648.0

HRMS (ESI): Calcd for $C_{24}H_{31}ClO_3Na$ $[M+Na]^+$: 425.1854, found 425.1846.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-3-(trifluoromethyl)benzene (**3.3s**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chloro-3-(trifluoromethyl)benzene (73 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-chloro-3-(trifluoromethyl)benzene (125 mg, 0.302 mmol, 61%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.15 (3% Et_2O in Cy).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.54 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 – 7.26 (m, 3H), 7.26 – 7.18 (m, 3H), 4.60 (t, *J* = 7.7 Hz, 1H), 3.28 (t, *J* = 6.5 Hz, 2H), 2.10 – 1.98 (m, 2H), 1.52 – 1.45 (m, 2H), 1.40 – 1.28 (m, 4H), 1.15 (s, 9H).

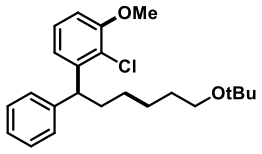
^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) 145.3, 143.1, 132.1, 129.0 (q, *J* = 30.6 Hz), 128.6, 128.3, 126.63, 126.6, 125.6 (q, *J* = 5.6 Hz), 123.2 (q, *J* = 273.2 Hz), 72.6, 61.5, 46.5, 35.7, 30.5, 30.5, 27.7, 26.3.

^{19}F{^{1}H}-NMR (470 MHz, $CDCl_3$): δ (ppm) -62.36.

IR (neat): ν (cm^{-1}2934.1, 2862.1, 1586.3, 1430.2, 1315.5, 1137.8, 1095.0, 698.5.

HRMS (ESI): Calcd for $C_{23}H_{28}ClF_3ONa$ $[M+Na]^+$: 435.1673, found 435.1670.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-3-methoxybenzene (**3.3t**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chloro-3-methoxybenzene (**S1d**, 111 mg, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-chloro-3-methoxybenzene (136 mg, 0.362 mmol, 73%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.35 (5% EtOAc in Cy).

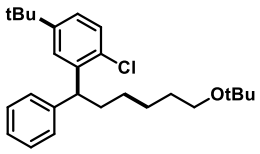
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27 – 7.24 (m, 4H), 7.20 – 7.13 (m, 2H), 6.92 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.4 Hz, 1H), 4.53 (t, *J* = 7.7 Hz, 1H), 3.87 (s, 3H), 3.28 (t, *J* = 6.5 Hz, 2H), 2.07 – 1.98 (m, 2H), 1.49 – 1.30 (m, 6H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 155.3, 144.4, 144.0, 128.4, 128.3, 127.0, 126.3, 122.8, 120.5, 109.6, 72.5, 61.6, 56.3, 46.8, 35.6, 30.6, 27.8, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2935.5, 1574.1, 1362.5, 1269.7, 1196.7, 1071.1, 908.0, 728.5, 647.6.

HRMS (ESI): Calcd for $C_{23}H_{31}ClO_2Na$ $[M+Na]^+$: 397.1905, found 397.1898.

2-(6-(*tert*-Butoxy)-1-phenylhexyl)-4-(*tert*-butyl)-1-chlorobenzene (**3.3u**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 2-bromo-4-(*tert*-butyl)-1-chlorobenzene (124 mg, 0.500 mmol, 1.0 equiv) to obtain 2-(6-(*tert*-butoxy)-1-phenylhexyl)-4-(*tert*-butyl)-1-chlorobenzene (115 mg, 0.287 mmol, 57%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.18 (1% Et_2O in Cy).

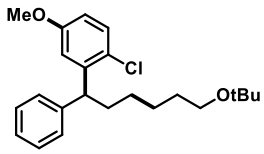
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (d, *J* = 2.4 Hz, 1H), 7.27 – 7.22 (m, 4H), 7.22 – 7.14 (m, 2H), 7.12 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.42 (t, *J* = 7.7 Hz, 1H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.02 (tt, *J* = 7.7 Hz, 2H), 1.52 – 1.43 (m, 2H), 1.41 – 1.30 (m, 4H), 1.27 (s, 9H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 149.9, 144.1, 141.7, 131.4, 129.1, 128.4, 128.3, 126.2, 125.6, 124.4, 72.5, 61.6, 47.0, 35.7, 34.7, 31.5, 30.6, 27.8, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2969.5, 1479.0, 1362.8, 1197.2, 1080.4, 907.6, 820.0, 729.7, 648.4.

HRMS (ESI): Calcd for $C_{26}H_{37}ClONa$ $[M+Na]^+$: 423.2425, found 423.2420.

2-(6-(*tert*-Butoxy)-1-phenylhexyl)-1-chloro-4-methoxybenzene (**3.3v**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 2-bromo-1-chloro-4-

methoxybenzene (68 µL, 0.500 mmol, 1.0 equiv) to obtain 2-(6-(*tert*-butoxy)-1-phenylhexyl)-1-chloro-4-methoxybenzene (120 mg, 0.320 mmol, 64%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.35 (5% EtOAc in Cy).

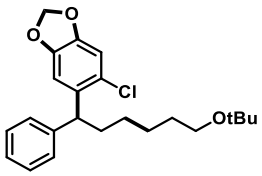
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29 – 7.25 (m, 4H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.20 – 7.15 (m, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.66 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.41 (t, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 3.29 (t, *J* = 6.6 Hz, 2H), 2.05 – 1.96 (m, 2H), 1.53 – 1.46 (m, 2H), 1.41 – 1.29 (m, 4H), 1.16 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.5, 143.8, 143.8, 130.2, 128.5, 128.3, 126.3, 125.9, 114.9, 112.2, 72.5, 61.6, 55.6, 46.9, 35.5, 30.6, 27.7, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2934.2, 2861.1, 1597.6, 1471.9, 1361.6, 1291.0, 1234.6, 1197.4, 1081.1, 1026.1, 731.5.

HRMS (ESI): Calcd for $C_{23}H_{31}ClO_2Na$ $[M+Na]^+$: 397.1905, found 397.1897.

5-(6-(*tert*-Butoxy)-1-phenylhexyl)-6-chlorobenzo-1,3-dioxole (**3.3w**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 5-Bromo-6-chloro-1,3-benzodioxole (118 mg, 0.500 mmol, 1.0 equiv) to obtain 5-(6-(*tert*-butoxy)-1-phenylhexyl)-6-chlorobenzo-1,3-dioxole (118 mg, 0.304 mmol, 61%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.14 (2.5% EtOAc in Cy).

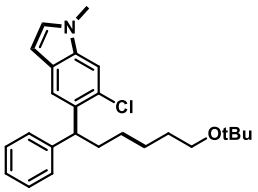
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 – 7.21 (m, 4H), 7.19 – 7.14 (m, 1H), 6.80 (s, 1H), 6.73 (s, 1H), 5.91 (dd, *J* = 14.0, 1.4 Hz, 2H), 4.40 (t, *J* = 7.7 Hz, 1H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.05 – 1.87 (m, 2H), 1.52 – 1.45 (m, 2H), 1.40 – 1.27 (m, 4H), 1.16 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.0, 146.3, 144.1, 136.1, 128.5, 128.1, 126.3, 125.6, 109.9, 108.1, 101.7, 72.5, 61.6, 46.4, 35.5, 30.6, 27.7, 27.6, 26.4.

IR (neat): ν (cm^{-1}) 2932.9, 1727.4, 1601.2, 1477.5, 1362.0, 1231.7, 1081.4, 1037.9, 934.0, 863.5.

HRMS (ESI): Calcd for $C_{23}H_{29}ClO_3Na$ $[M+Na]^+$: 411.1697, found 411.1692.

5-(6-(*tert*-Butoxy)-1-phenylhexyl)-6-chloro-1-methyl-1H-indole (**3.3x**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 5-bromo-6-chloro-1-methyl-1H-indole (**S1b**, 122 mg, 0.500 mmol, 1.0 equiv) to obtain 5-(6-(*tert*-butoxy)-1-phenylhexyl)-6-chloro-1-methyl-1H-indole (105 mg, 0.264 mmol, 53%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.18 (5% EtOAc in Cy).

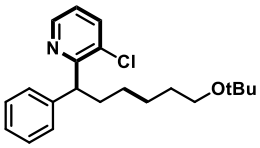
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (s, 1H), 7.32 – 7.30 (m, 1H), 7.28 – 7.21 (m, 4H), 7.16 – 7.10 (m, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.40 (dd, *J* = 3.1, 0.9 Hz, 1H), 4.52 (t, *J* = 7.7 Hz, 1H), 3.70 (s, 3H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.53 – 1.45 (m, 2H), 1.42 – 1.32 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 145.2, 135.8, 133.5, 129.7, 128.6, 128.4, 128.3, 127.7, 125.9, 120.2, 110.1, 101.1, 72.5, 61.7, 46.8, 36.4, 33.0, 30.7, 27.9, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2932.5, 2860.1, 1482.5, 1453.3, 1361.3, 1239.1, 1197.2, 1081.4, 1018.0, 909.4, 837.5, 721.7, 643.2.

HRMS (ESI): Calcd for $C_{25}H_{32}ClNONa$ $[M+Na]^+$: 420.2065, found 420.2059.

2-(6-(*tert*-Butoxy)-1-phenylhexyl)-3-chloropyridine (**3.3y**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 2-bromo-3-chloropyridine (96.2 mg, 0.500 mmol, 1.0 equiv) to obtain 2-(6-(*tert*-butoxy)-1-phenylhexyl)-3-chloropyridine (67.0 mg, 0.194 mmol, 39%) as a slightly yellow oil.

rr: (benzylic vs. others) 92:8.

Rf = 0.1 (5% EtOAc in Cy).

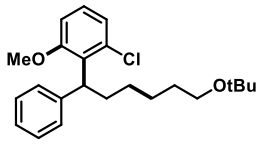
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.52 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.28 – 7.23 (m, 2H), 7.19 – 7.14 (m, 1H), 7.05 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.56 (t, *J* = 7.6 Hz, 1H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.36 – 2.05 (m, 2H), 1.52 – 1.44 (m, 2H), 1.38 – 1.22 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 160.4, 147.4, 143.0, 137.0, 131.7, 128.5, 128.3, 126.5, 122.2, 72.5, 61.6, 48.5, 35.4, 30.6, 27.7, 27.7, 26.3.

IR (neat): ν (cm^{-1}) 3028.6, 2931.4, 2858.5, 1573.3, 1421.8, 1361.7, 1197.1, 1081.2, 1028.5, 794.7, 745.9, 698.5.

HRMS (ESI): Calcd for $C_{21}H_{28}ClNOH$ $[M+H]^+$: 346.1932, found 346.1936.

2-(6-(*tert*-Butoxy)-1-phenylhexyl)-1-chloro-3-methoxybenzene (**3.3z**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 2-bromo-1-chloro-3-methoxybenzene (**S1e**, 111 mg, 0.500 mmol, 1.0 equiv) to obtain 2-(6-(*tert*-butoxy)-1-phenylhexyl)-1-chloro-3-methoxybenzene (47 mg, 0.126 mmol, 25%) as a colourless oil which could not be further purified.

rr: (benzylic vs. others) >95:5.

Rf = 0.35 (5% EtOAc in Cy).

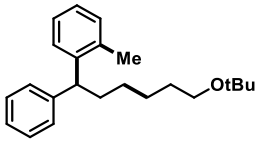
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 – 7.30 (m, 2H), 7.25 – 7.13 (m, 3H), 7.08 (t, *J* = 8.1 Hz, 1H), 6.99 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 4.86 – 4.74 (m, 1H), 3.63 (s, 3H), 3.29 (t, *J* = 6.6 Hz, 2H), 2.36 – 2.15 (m, 2H), 1.53 – 1.48 (m, 2H), 1.42 – 1.31 (m, 4H), 1.17 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 159.4, 144.2, 135.3, 131.6, 128.5, 128.4, 128.1, 127.8, 127.7, 125.6, 72.5, 61.7, 55.8, 44.0, 35.8, 30.7, 28.1, 27.7, 26.6.

IR (neat): ν (cm^{-1}) 2932.2, 2861.0, 1584.3, 1461.1, 1258.3, 1197.7, 1081.6, 1039.6, 862.9, 738.8, 697.6.

HRMS (ESI): Calcd for $C_{23}H_{31}ClO_2Na$ $[M+Na]^+$: 397.1905, found 397.1902.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-methylbenzene (**3.3aa**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-methylbenzene (60 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-methylbenzene (130 mg, 0.400 mmol, 80%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.18 (1% Et_2O in Cy).

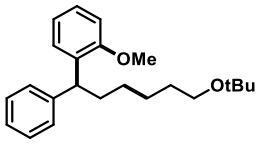
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 (d, *J* = 7.7 Hz, 1H), 7.27 – 7.13 (m, 6H), 7.12 – 7.08 (m, 2H), 4.07 (t, *J* = 7.6 Hz, 1H), 3.28 (t, *J* = 6.6 Hz, 2H), 2.26 (s, 3H), 2.05 – 1.95 (m, 2H), 1.53 – 1.42 (m, 2H), 1.39 – 1.26 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 145.0, 143.1, 136.4, 130.6, 128.4, 128.3, 126.8, 126.1, 126.0, 125.9, 72.5, 61.6, 47.0, 36.4, 30.6, 28.0, 27.7, 26.5, 20.1.

IR (neat): ν (cm^{-1}) 3025.0, 2931.3, 2859.2, 1601.1, 1457.5, 1389.1, 1198.2, 1084.0, 748.5, 732.5.

HRMS (ESI): Calcd for $C_{23}H_{32}ONa$ $[M+Na]^+$: 347.2345, found 347.2344.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-methoxybenzene (**3.3ab**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-methoxybenzene (62 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-methoxybenzene (97 mg, 0.285 mmol, 57%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.4 (5% EtOAc in Cy).

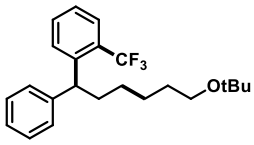
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27 – 7.19 (m, 5H), 7.17 – 7.09 (m, 2H), 6.90 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.3, 1.2 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 3.27 (t, *J* = 6.7 Hz, 2H), 2.05 – 1.94 (m, 2H), 1.52 – 1.44 (m, 2H), 1.39 – 1.25 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 157.2, 145.4, 133.9, 128.3, 128.2, 127.7, 127.0, 125.8, 120.6, 110.8, 72.5, 61.7, 55.6, 43.2, 35.2, 30.6, 28.0, 27.7, 26.4.

IR (neat): ν (cm^{-1}) 2933.3, 1733.6, 1599.2, 1491.0, 1240.6, 1197.2, 1081.0, 1030.7, 908.9, 731.0, 648.3.

HRMS (ESI): Calcd for $C_{23}H_{32}O_2Na$ $[M+Na]^+$: 363.2295, found 363.2293.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-(trifluoromethyl)benzene (**3.3ac**)



The title compound was obtained following general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-2-(trifluoromethyl)benzene (76 µL, 0.500 mmol, 1.0 equiv) to obtain 1-(6-(*tert*-butoxy)-1-phenylhexyl)-2-(trifluoromethyl)benzene (122 mg, 0.323 mmol, 65%) as a colourless oil.

rr: (benzylic vs. others) >99:1.

Rf = 0.2 (3% Et_2O in Cy).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.30 – 7.25 (m, 5H), 7.19 – 7.15 (m, 1H), 4.41 (t, *J* = 7.6 Hz, 1H), 3.27 (t, *J* = 6.5 Hz, 2H), 2.14 – 1.93 (m, 2H), 1.51 – 1.45 (m, 2H), 1.40 – 1.27 (m, 4H), 1.15 (s, 9H).

^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ (ppm) 144.7, 143.9, 132.1, 129.5, 128.5, 128.3 (q, *J* = 25.3 Hz), 128.12, 126.4, 126.0, 125.9 (q, *J* = 5.9 Hz), 124.8 (q, *J* = 274.2 Hz), 72.6, 61.5, 45.6, 36.8, 30.5, 27.8, 27.7, 26.4.

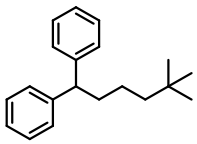
^{19}F{^{1}H}-NMR (476 MHz, $CDCl_3$): δ (ppm) -57.74.

IR (neat): ν (cm^{-1}) 2932.6, 2862.7, 1734.6, 1605.5, 1454.5, 1362.1, 1311.2, 1198.2, 1120.2, 876.9, 766.9, 699.3, 668.3.

HRMS (ESI): Calcd for $C_{23}H_{29}F_3OAg$ $[M+Ag]^+$: 485.1216, found 485.1209.

6.3.4. Deprotection and postfunctionalisation

(5,5-Dimethylhexane-1,1-diyl)dibenzene (**3.22**)



Prepared following a modified reported procedure.[221] 1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**, 150 mg, 0.500 mmol, 1.0 equiv), NaOtBu (50.5 mg, 0.525 mmol. 1.05 equiv), [(IPr)Pd(allyl)Cl] (1.43 mg, 2.50 µmol, 0.5 mol%) and technical grade iPrOH (1.0 mL) were charged in a microwave vial which was flushed with Argon and then sealed with a cap fitted with a septum. The vial was then placed in a microwave reactor set at 120 °C for 4 min. The reaction mixture was filtered over Celite® to obtain (5,5-dimethylhexane-1,1-diyl)dibenzene (133 mg, 0.500 mmol, quant.) as a colourless oil.

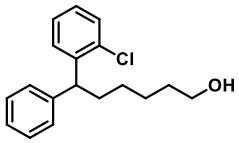
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 – 7.19 (m, 8H), 7.19 – 7.11 (m, 2H), 3.91 (t, *J* = 7.8 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.25 – 1.17 (m, 4H), 0.80 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 145.5, 128.5, 128.0, 126.1, 51.4, 44.3, 36.8, 30.5, 29.5, 23.1.

IR (neat): ν (cm^{-1}) 3026.9, 2950.4, 1600.4, 1469.9, 1364.1, 1249.8, 747.3, 698.7.

HRMS (ESI): Calcd for $C_{20}H_{26}Ag$ $[M+Ag]^+$: 373.1080, found 373.1073.

6-(2-Chlorophenyl)-6-phenylhexan-1-ol (**3.23**)



1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chlorobenzene (**3.3b**, 20.0 mg, 0.058 mmol, 1.0 equiv) was dissolved in trifluoroacetic acid (2.0 mL) at 0 °C and the reaction mixture was allowed to warm to 25 °C and stirred for 1 h. Water (20 mL) was then slowly added to the reaction mixture, and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles removed under reduced pressure to obtain 6-(2-chlorophenyl)-6-phenylhexan-1-ol (17.0 mg, 0.059 mmol, quant.) as a colourless oil.

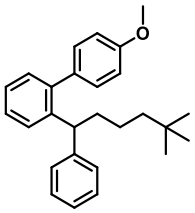
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 – 7.15 (m, 8H), 7.15 – 7.05 (m, 1H), 4.47 (t, *J* = 7.7 Hz, 1H), 4.30 (t, *J* = 6.6 Hz, 2H), 2.09 – 1.97 (m, 2H), 1.71 (tt, *J* = 7.8, 6.6 Hz, 2H), 1.44 – 1.20 (m, 5H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 143.6, 142.4, 134.3, 129.8, 128.5, 128.5, 128.3, 127.5, 127.1, 126.5, 68.3, 46.6, 35.3, 28.1, 27.4, 25.6.

IR (neat): ν (cm^{-1}) 3730.4, 2934.0, 1784.6, 1469.6, 1350.3, 1220.1, 1150.8, 1036.0, 751.0.

HRMS (ESI): Calcd for $C_{18}H_{21}ClOAg$ $[M+Ag]^+$: 395.0326, found 395.0321.

2-(5,5-Dimethyl-1-phenylhexyl)-4'-methoxy-1,1'-biphenyl (**3.24**)



Prepared according to a modified procedure.[223] 1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**, 75.2 mg, 0.250 mmol, 1.0 equiv), 4-methoxyphenylboronic acid (41.8 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.25 mg, 0.010 mmol, 4 mol%), SPhos (10.3 mg, 0.025 mmol, 10 mol%) and K_3PO_4 (159 mg, 0.750 mmol, 3.0 equiv) were charged in a vial, which was purged and filled with Argon three times. THF (0.9 mL) and water (0.3 mL) were added and the septum exchange with a cap. The vial was placed in a heating block set at 60 °C for 18 h. The reaction mixture was then filtered over Celite® and the volatiles removed under reduced pressure. The crude product was purified by FCC (1% Et_2O in cyclohexane) to obtain 2-(5,5-dimethyl-1-phenylhexyl)-4'-methoxy-1,1'-biphenyl (86.0 mg, 0.231 mmol, 92%) as a colourless oil.

Rf = 0.2 (1% Et_2O in Cy).

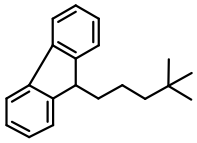
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 7.25 – 7.14 (m, 4H), 7.14 – 7.03 (m, 5H), 6.95 – 6.87 (m, 2H), 4.10 (t, *J* = 7.7 Hz, 1H), 3.83 (s, 3H), 1.99 – 1.85 (m, 2H), 1.16 – 1.01 (m, 4H), 0.75 (s, 9H).

$^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ (ppm) 158.7, 145.7, 142.8, 142.2, 134.5, 130.7, 130.4, 128.3, 128.1, 127.5, 127.4, 125.8, 125.7, 113.4, 55.4, 46.4, 44.1, 37.9, 30.4, 29.5, 23.0.

IR (neat): ν (cm^{-1}) 2953.1, 1611.6, 1515.5, 1477.9, 1243.0, 1177.1, 1038.2, 906.1, 727.0.

HRMS (ESI): Calcd for $C_{27}H_{32}ONa$ $[M+Na]^+$: 395.2345, found 395.2342.

9-(4,4-Dimethylpentyl)-9H-fluorene (**3.25c**)



Prepared according to a modified procedure.[224] 1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**, 150 mg, 0.500 mmol, 1.0 equiv), CsOPiv (351 mg, 1.50 mmol, 3.0 equiv), $Pd(OAc)_2$ (3.37 mg, 0.015 mmol, 3 mol%) and tricyclohexylphospine (8.41 mg, 0.030 mmol, 6 mol%) were charged in a vial, which was purged and filled with Argon three times. THF (2.0 mL) was added and the septum exchanged with a cap. The vial was then placed in a heating block set at 120 °C with vigorous stirring for 12 h. The reaction mixture was then filtered over Celite® and the volatiles removed under reduced pressure. The crude product was then purified by FCC (cyclohexane) to obtain 9-(4,4-dimethylpentyl)-9H-fluorene (132 mg, 0.500 mmol, quant.) as a colourless oil.

Rf = 0.8 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 7.4 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.32 (dd, *J* = 7.3 Hz, 2H), 7.27 (dd, *J* = 7.2 Hz, 2H), 3.92 (t, *J* = 6.3 Hz, 1H), 1.88 (t, *J* = 7.8, 7.0 Hz, 2H), 1.37 – 1.25 (m, 2H), 1.25 – 1.11 (m, 2H), 0.81 (s, 9H).

^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 147.9, 141.2, 127.0, 126.9, 124.5, 119.9, 47.7, 44.6, 34.6, 30.5, 29.6, 21.6.

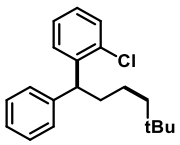
IR (neat): ν (cm^{-1}) 2950.4, 1473.9, 1246.6, 1029.8, 934.9, 735.7, 661.9.

HRMS (ESI): Calcd for $C_{20}H_{24}Ag$ $[M+Ag]^+$: 371.0923, found 371.0918.

6.3.5. Mechanistic study

6.3.5.1. Palladium catalysed migratory arylation from a regioisomeric mixture of alkenes

1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**)



The title compound was obtained following the adapted general procedure **J** from (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**, 56.5 mg, 0.300 mmol, 0.6 equiv), (*Z*)-(5,5-dimethylhex-2-en-1-yl)benzene (**3.1l**, 56.5 mg, 0.300 mmol, 0.6 equiv), and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain 1-chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (150 mg,

0.500 mmol, quant.) as a colourless oil. Spectroscopic data are consistent with those reported above.

rr: (benzylic vs. others) >99:1.

Rf = 0.84 (cyclohexane).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 – 7.26 (m, 5H), 7.26 – 7.14 (m, 3H), 7.14 – 7.06 (m, 1H), 4.50 (t, *J* = 7.7 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.29 – 1.18 (m, 4H), 0.82 (s, 9H).

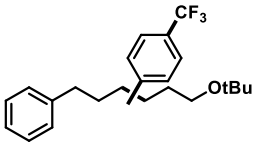
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ (ppm) 144.0, 142.7, 134.4, 129.8, 128.6, 128.4, 128.3, 127.3, 127.0, 126.3, 46.8, 44.2, 36.5, 30.5, 29.5, 22.9.

IR (neat): ν (cm^{-1}) 3027.1, 2951.6, 1600.4, 1470.2, 1364.2, 1249.4, 907.4, 731.0, 670.0.

HRMS (ESI): Calcd for $C_{20}H_{26}Ag$ $[M+Ag]^+$: 373.1080, found 373.1079.

6.3.5.2. Influence on the regioselectivity

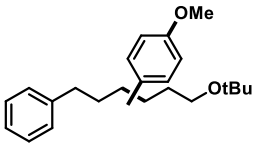
1-(6-(*tert*-Butoxy)-1-phenylhexyl)-4-(trifluoromethyl)benzene (**3.3ad**)



The title compound was obtained as a regioisomeric mixture using general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-4-(trifluoromethyl)benzene (70 µL, 0.500 mmol, 1.0 equiv). The crude product was analyzed by GC-MS to determine the regioselectivity.

rr: (benzylic vs. others) 76:24.

1-(6-(*tert*-Butoxy)-1-phenylhexyl)-4-methoxybenzene (**3.3ae**)

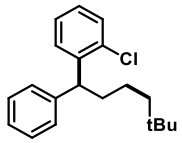


The title compound was obtained as a regioisomeric mixture using general procedure **J** from (*E*)-(6-(*tert*-butoxy)hex-3-en-1-yl)benzene (**3.1b**, 157 µL, 0.600 mmol, 1.2 equiv) and 1-bromo-4-methoxybenzene (63 µL, 0.500 mmol, 1.0 equiv). The crude product was analyzed by GC-MS to determine the regioselectivity.

rr: (benzylic vs. others) 60:40.

6.3.5.3. Crossover experiment

1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**)

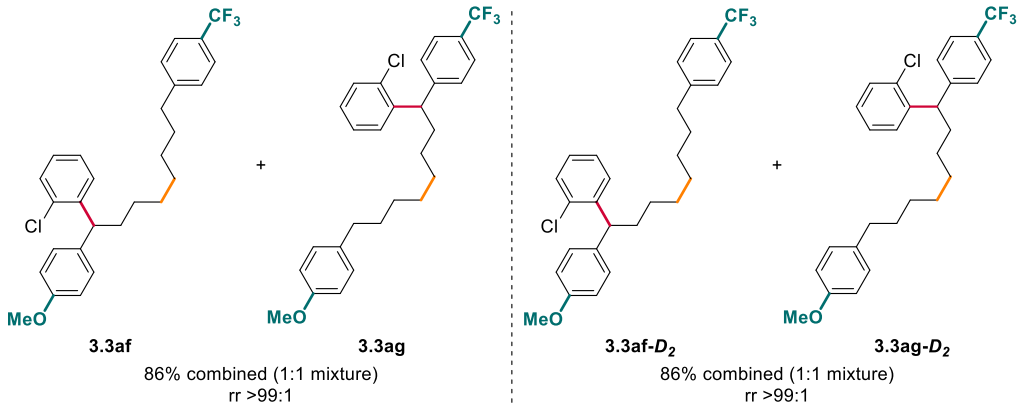


The title compound was obtained following the adapted general procedure **J** from (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**, 132 µl, 0.600 mmol, 1.2 equiv), and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv). (*Z*)-1-(5,5-dimethylhex-3-en-1-yl)-4-methoxybenzene (**3.1h**, 131 mg, 0.600 mmol, 1.2 equiv) was added to the reaction at the same time as the aryl bromide. The presence/absence of crossover product and the regioselectivity were analyzed by GC-MS. Dibromomethane (17.5 µL, 0.250 mmol, 0.5 equiv) was added as an internal standard and the yield determined by ^{1}H-NMR analysis. No crossover product was observed.

rr: (benzylic vs. others) >99:1.

^{1}H-NMR yield: quant.

6.3.5.4. Isotopic labelling experiment



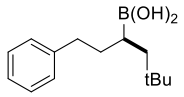
The title compounds were obtained following general procedure **J** from (*Z*)-1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl)benzene (**3.1r**, 217 mg, 0.600 mmol, 1.2 equiv) and 1-bromo-2-chlorobenzene (58 µL, 0.500 mmol, 1.0 equiv) to obtain a 1 to 1 mixture of 1-chloro-2-(1-(4-methoxyphenyl)-8-(4-(trifluoromethyl)phenyl)octyl)benzene (**3.3af**) and 1-chloro-2-(8-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)octyl)benzene (**3.3ag**) (202 mg, 0.424 mmol, 85%) as an inseparable colourless oil.

The same was performed using (*Z*)-1-methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl-4,5-d2)benzene (**3.1r-*D*$_2$**, 219 mg, 0.600 mmol, 1.2 equiv) to obtain a 1 to 1 mixture of 1-chloro-2-(1-(4-methoxyphenyl)-8-(4-(trifluoromethyl)phenyl)octyl)benzene (**3.3af-*D*$_2$**) and 1-chloro-2-(8-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)octyl)benzene (**3.3ag-*D*$_2$**) each bearing two deuterium atoms along the alkyl chain (185 mg, 0.388 mmol, 78%) as an inseparable colourless oil.

rr: >99:1

Rf = 0.4 (2% Et_2O in Cy).

6.3.5.5. Determination of organoborane specie



Identical to general procedure **J**, (*Z*)-(5,5-dimethylhex-3-en-1-yl)benzene (**1c**, 124 mg, 0.600 mmol, 1.2 equiv) was charged in an oven-dried 10 mL catalysis tube equipped with a stirring bar and septum, and then purged and filled with Argon three times. A borane dimethyl sulfide complex solution in toluene (2 M, 0.35 mL, 0.700 mmol, 1.4 equiv) was then added and the tube placed in a metal heating block set at 60 °C with stirring, fitted with a balloon. After 1 h water (0.10 mL, 5.55 mmol, 11.1 equiv) was added to the reaction mixture, which was further stirred at 60 °C for 1 h. The balloon was then swapped with a line from the Schlenk and the volatiles were removed under high vacuum at 60 °C for 1 h.

The crude product was then analyzed by ^{11}B-NMR. The range of the peak (19.49 ppm) is within the range of $RB(OH)_2$ (35 – 15 ppm), compared to $R_2B(OH)$ (40 – 60 ppm) and R_3B (80 – 90 ppm).[28] The absence of a second peak slightly upfield of the boronic acid despite using D_2O as solvent is also indicative for the absence of boroxine.

^{11}B-NMR (160 MHz, D_2O): δ (ppm) 19.49.

6.4. Benzylic Selective Migratory SMC – C(sp^2)-H Activation Cascade

6.4.1. General procedure for the screening of the reaction conditions

General Procedure **L**: One-Pot Hydroboration – Migratory Suzuki-Miyaura Coupling – C(sp^2)-H Activation cascade

The olefin (0.600 mmol, 1.2 equiv) was charged in an oven-dried 10 mL catalysis tube equipped with a stirring bar and septum, and then purged and filled with Argon three times. A borane dimethyl sulfide complex solution in toluene (2 M, 0.35 mL, 0.700 mmol, 1.4 equiv) was then added and the tube placed in a metal heating block set at 60 °C with stirring, fitted with a balloon. After 1 h water (0.10 mL, 5.55 mmol, 11.1 equiv) was added to the reaction mixture, which was further stirred at 60 °C for 1 h. The balloon was then swapped with a line from the Schlenk and the volatiles were removed under high vacuum at 60 °C for 1 h. After allowing the tube cool down to 25 °C it was transferred in a glovebox and $Pd(TFA)_2$ (8.31 mg, 0.025 mmol, 5 mol%), $(t\text{Bu})_2\text{PMe}\bullet\text{HBF}_4$ (18.6 mg, 0.075 mmol, 15 mol%), Cs_2CO_3 (489 mg, 1.50 mmol, 3.0 equiv) and aryl bromide (0.500 mmol, 1.0 equiv) (if solid) were charged in the catalysis tube. Outside of the glovebox, toluene (1.0 mL), water (0.1 mL) and the aryl bromide (0.500 mmol, 1.0 equiv) (if liquid) were added. The septum was rapidly exchanged for a screw cap, the catalysis tube sealed with Teflon-tape and then placed in a heating block set at 120 °C with vigorous stirring for 36 h. After this period the reaction mixture was allowed to cool to 25 °C and filtered over Celite® with EtOAc. The volatiles were removed under reduced pressure and the crude product was analyzed with GC-MS to determine the regioselectivity and yield.

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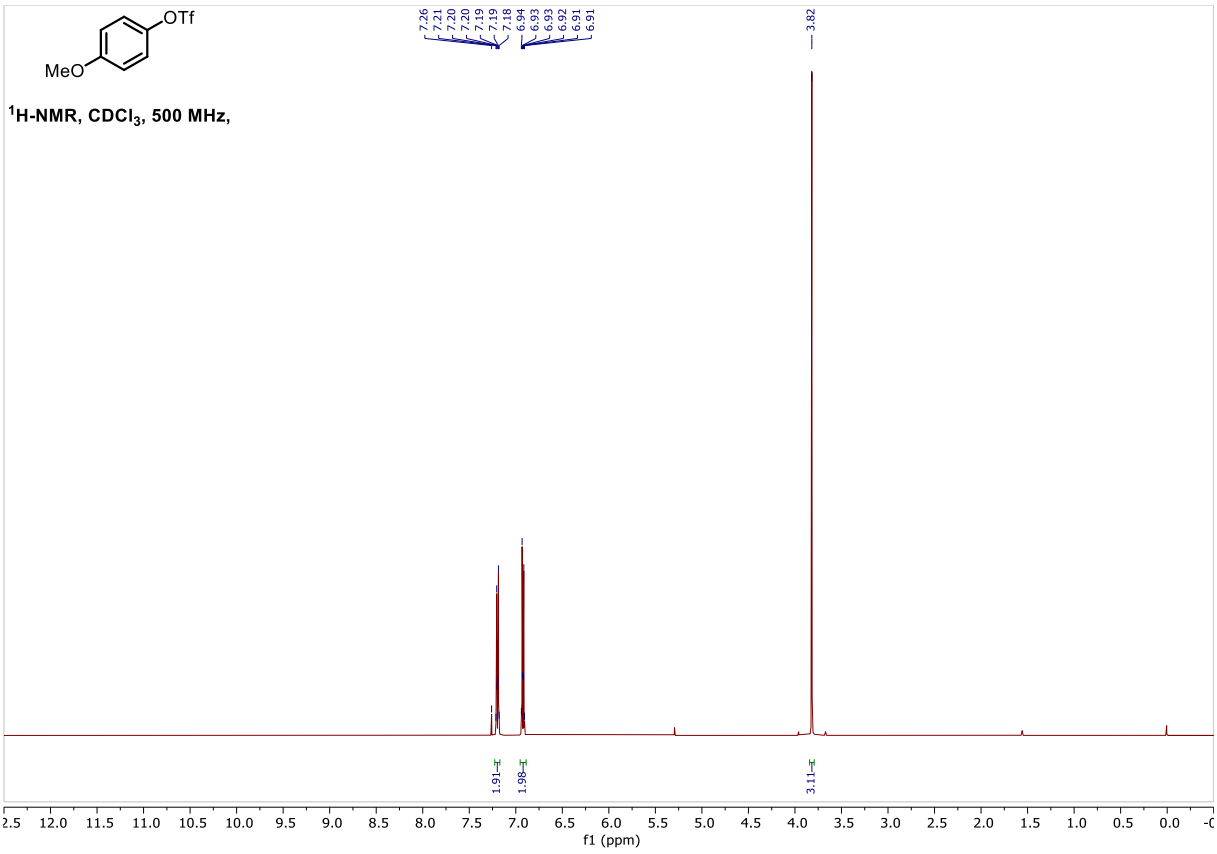
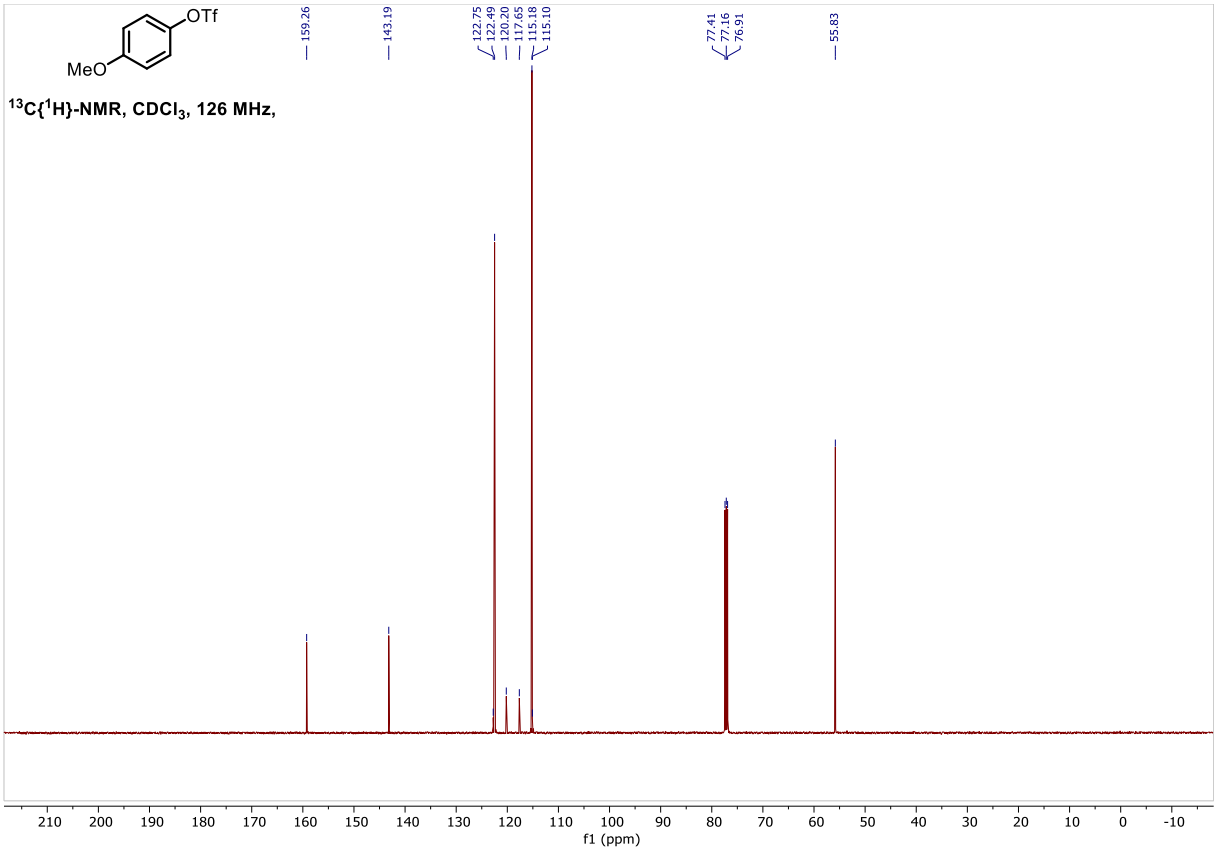
7. NMR Spectra of Compounds

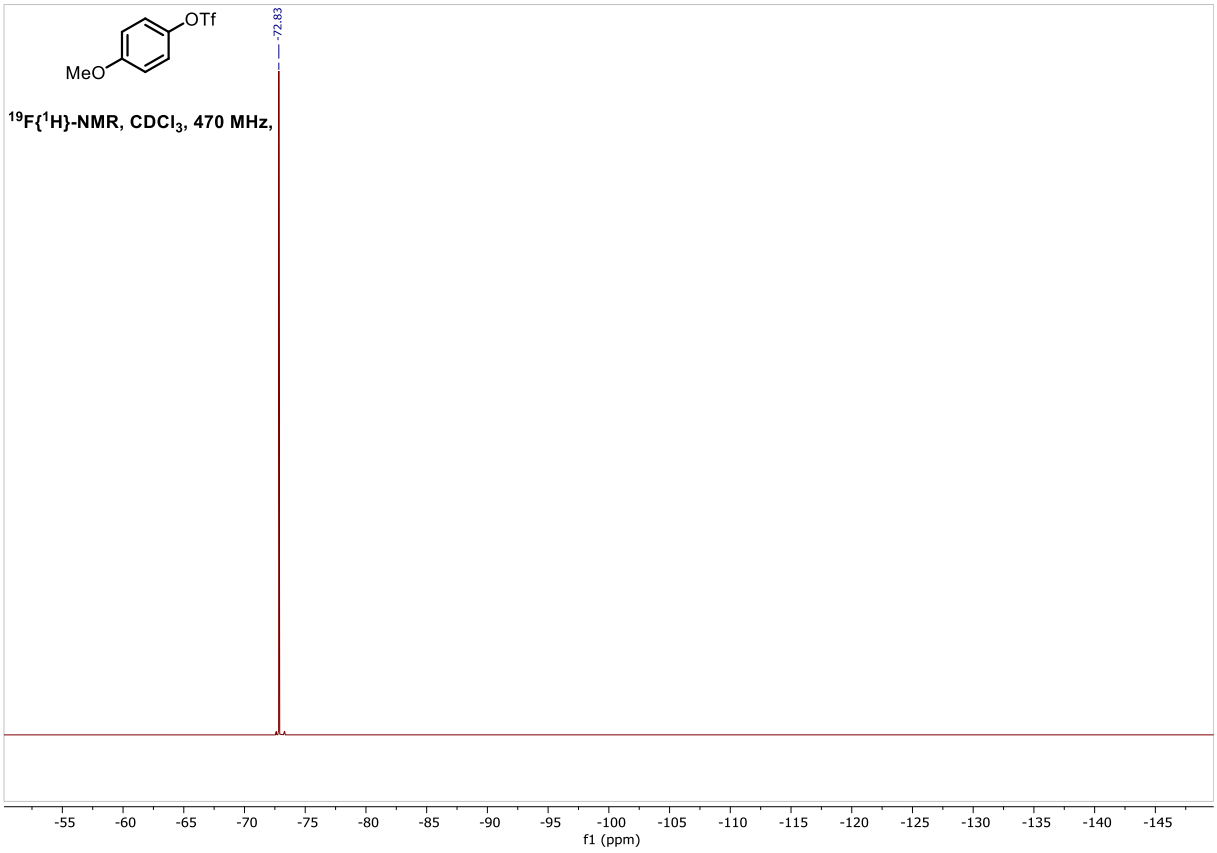
7.1. Terminal Selective SMC

4-Methoxyphenyl trifluoromethanesulfonate (**2.21a**)



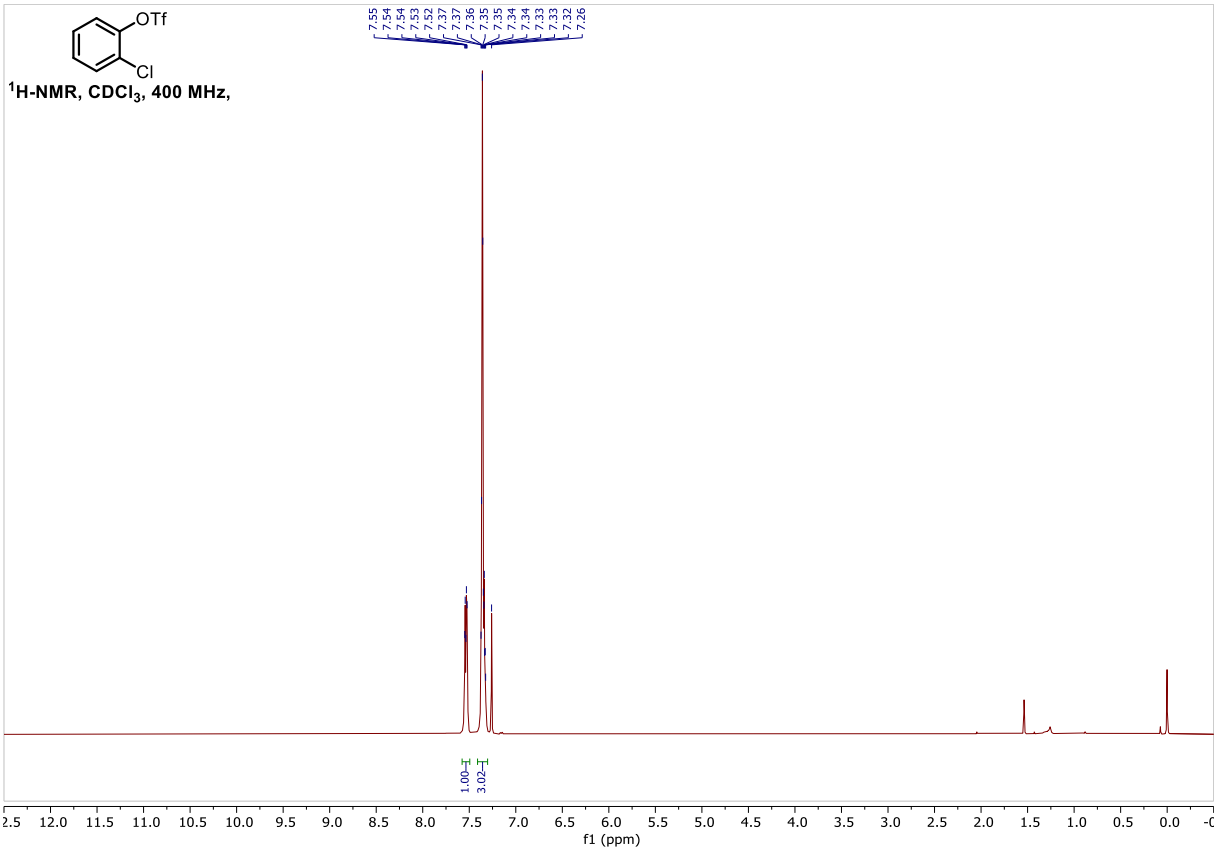


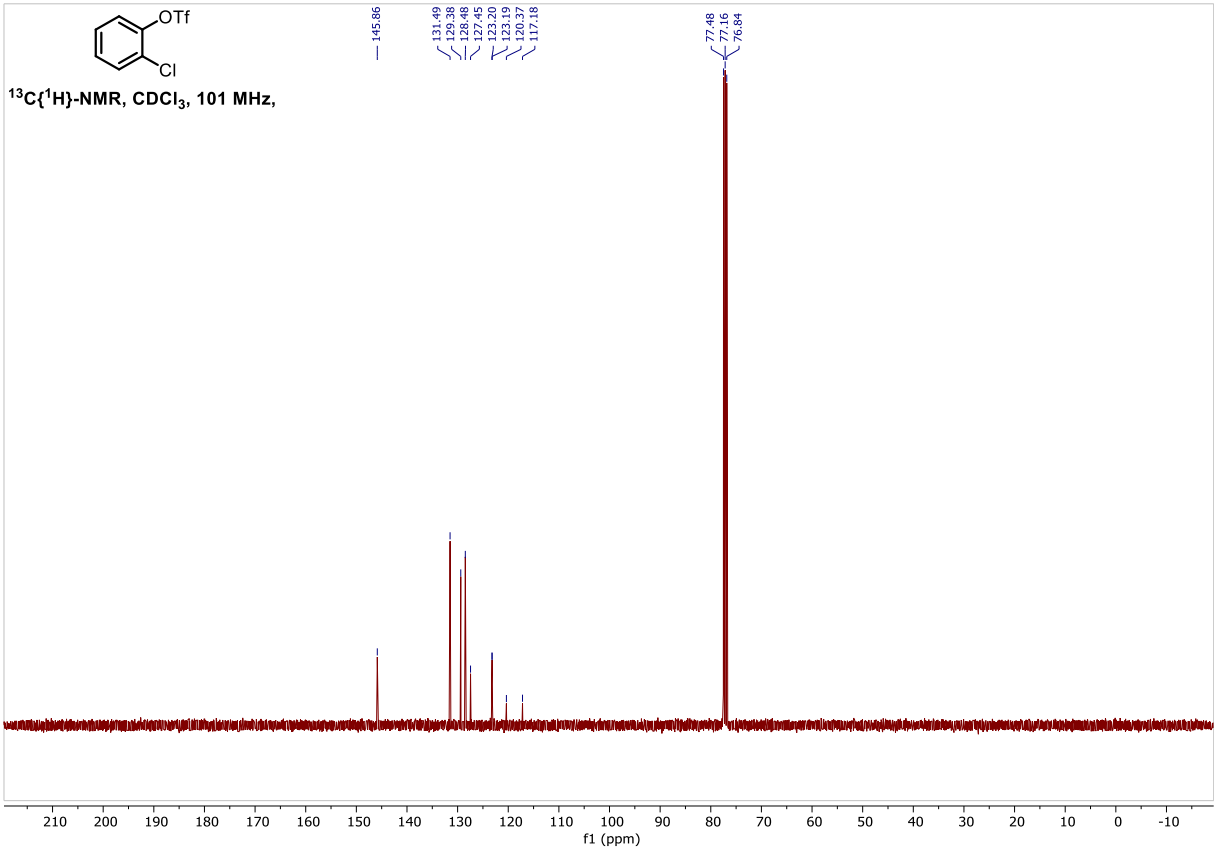
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

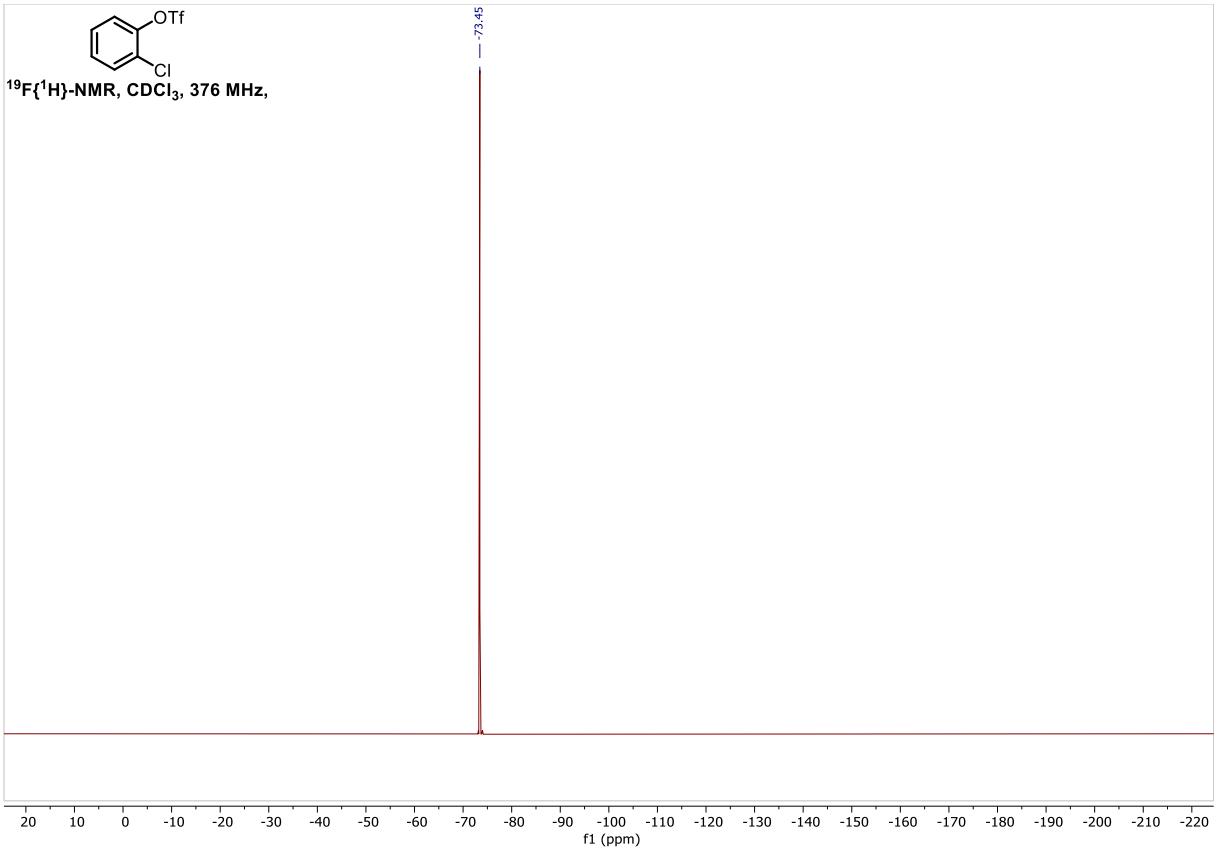


$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 470 MHz,

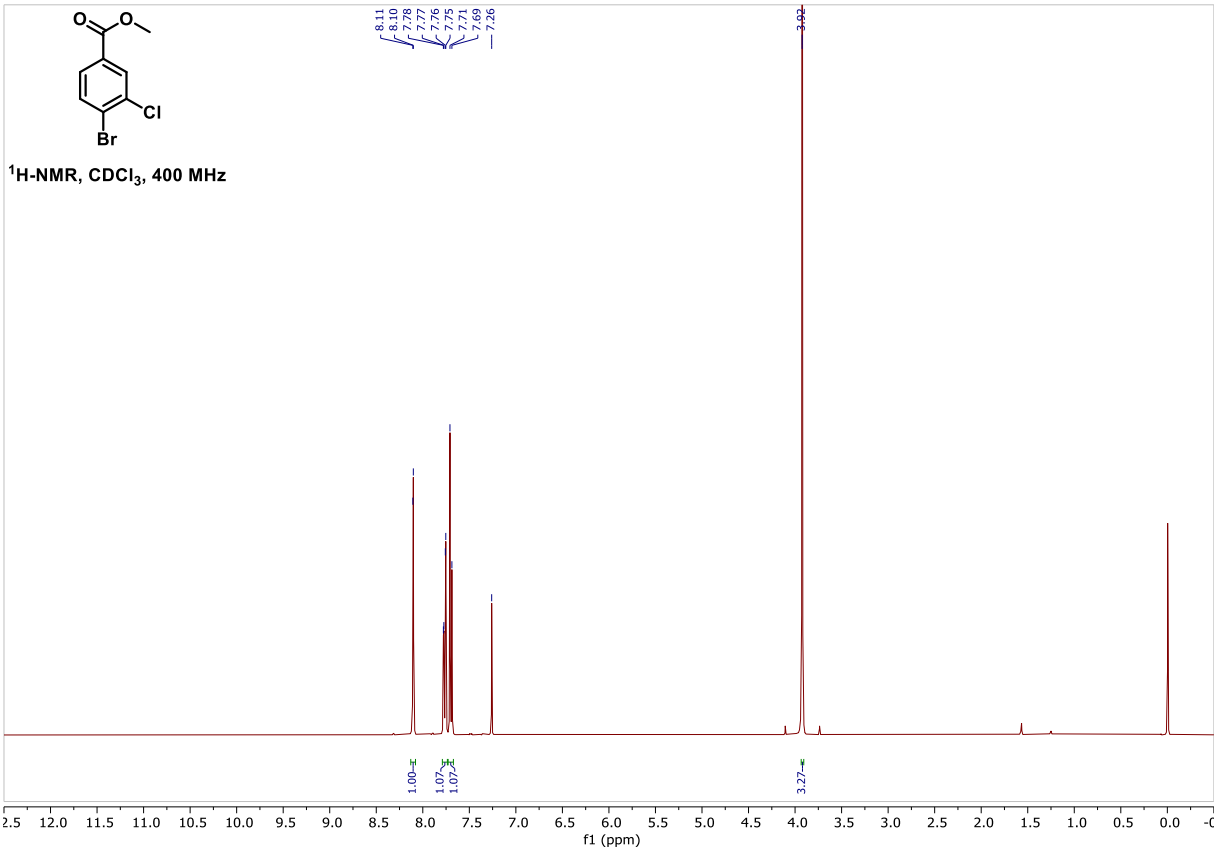
2-Chlorophenyl trifluoromethanesulfonate (**2.21h**)

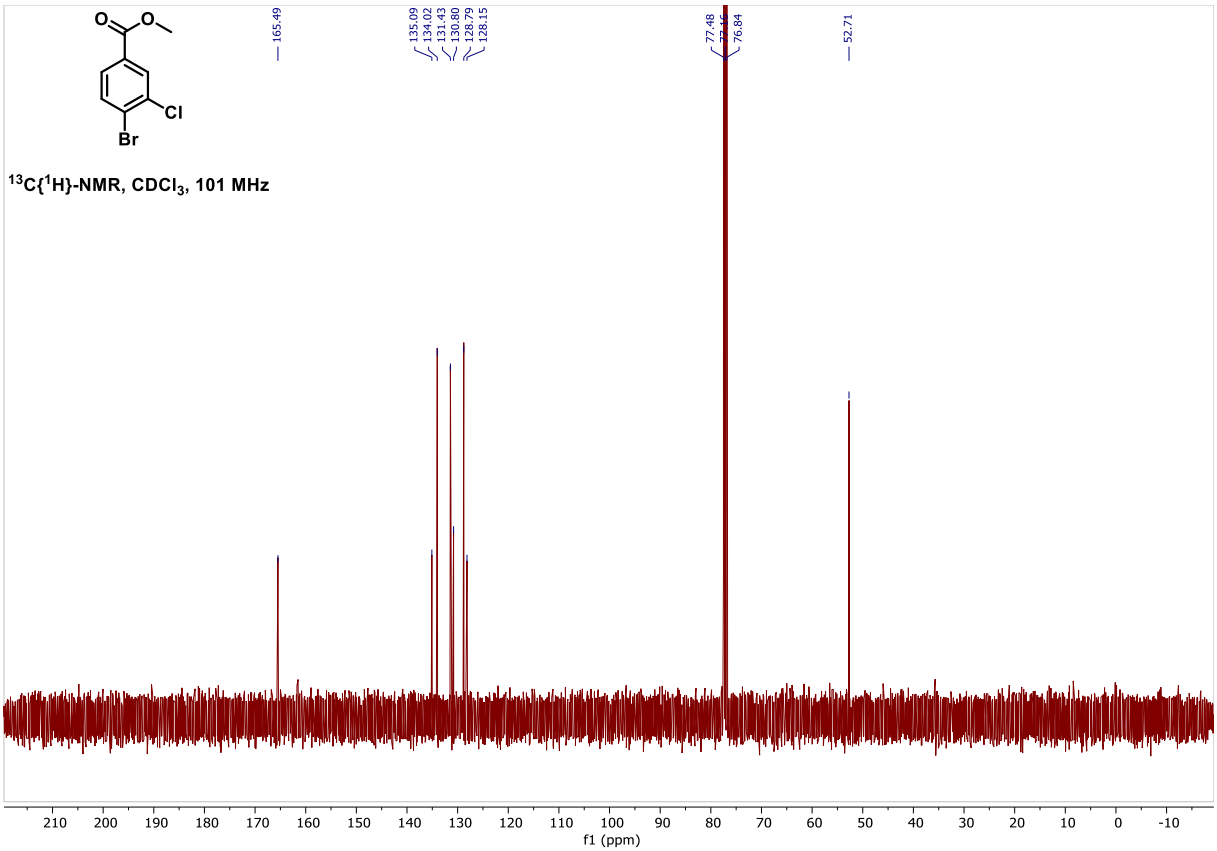




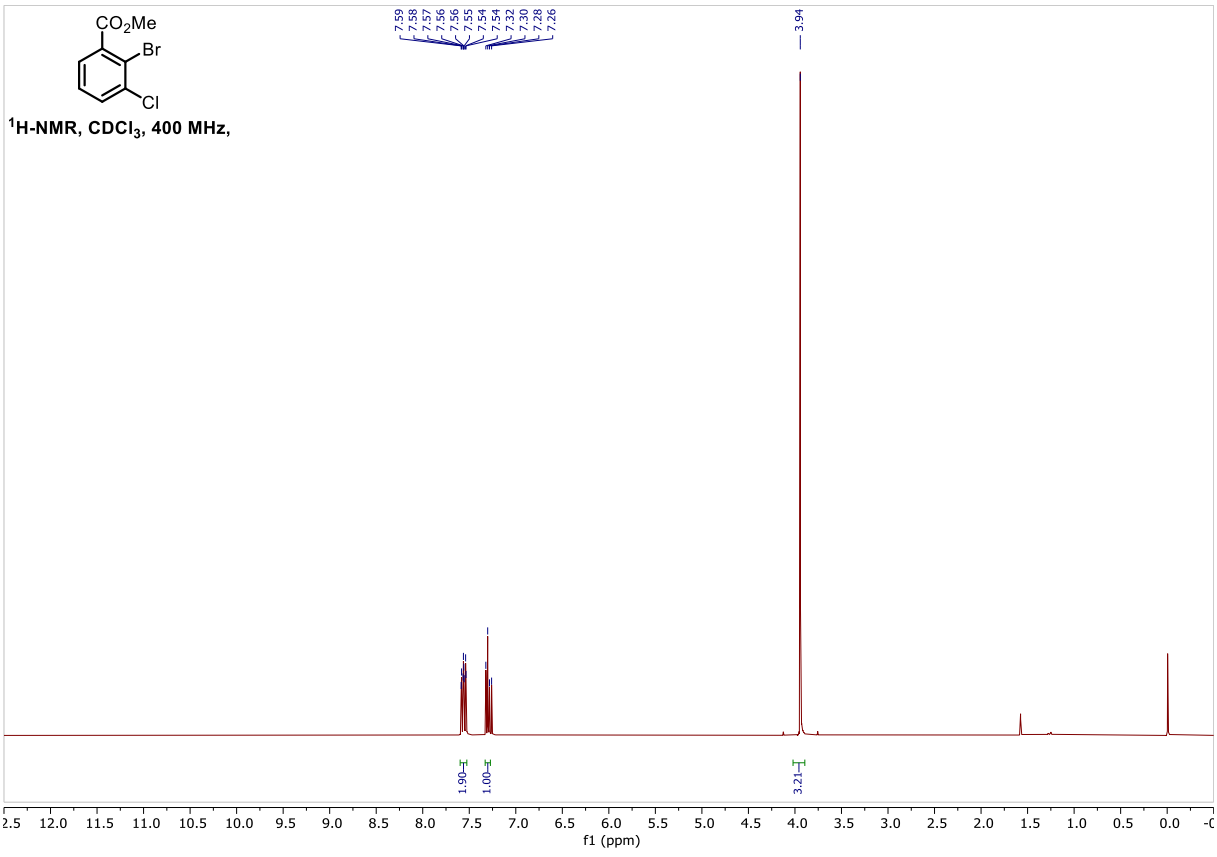


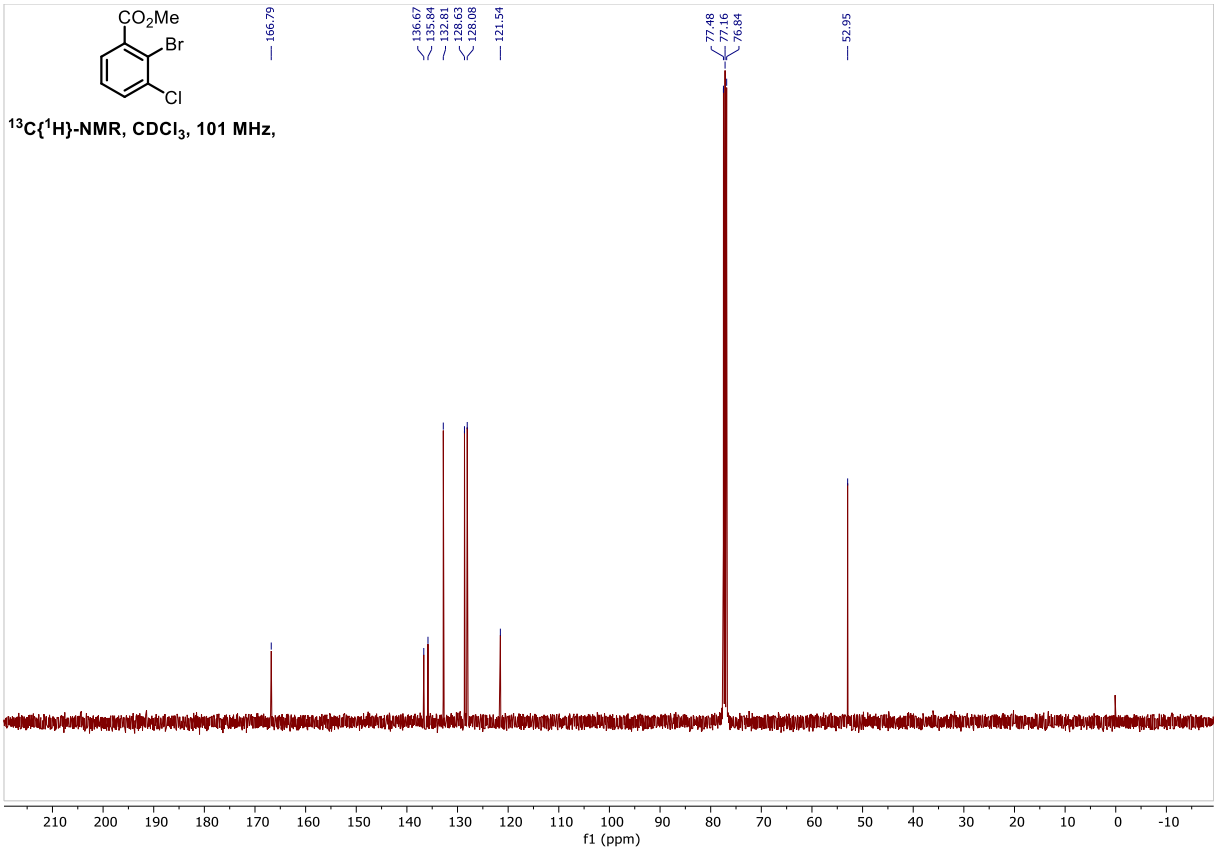
Methyl 4-bromo-3-chlorobenzoate (**2.2i**)



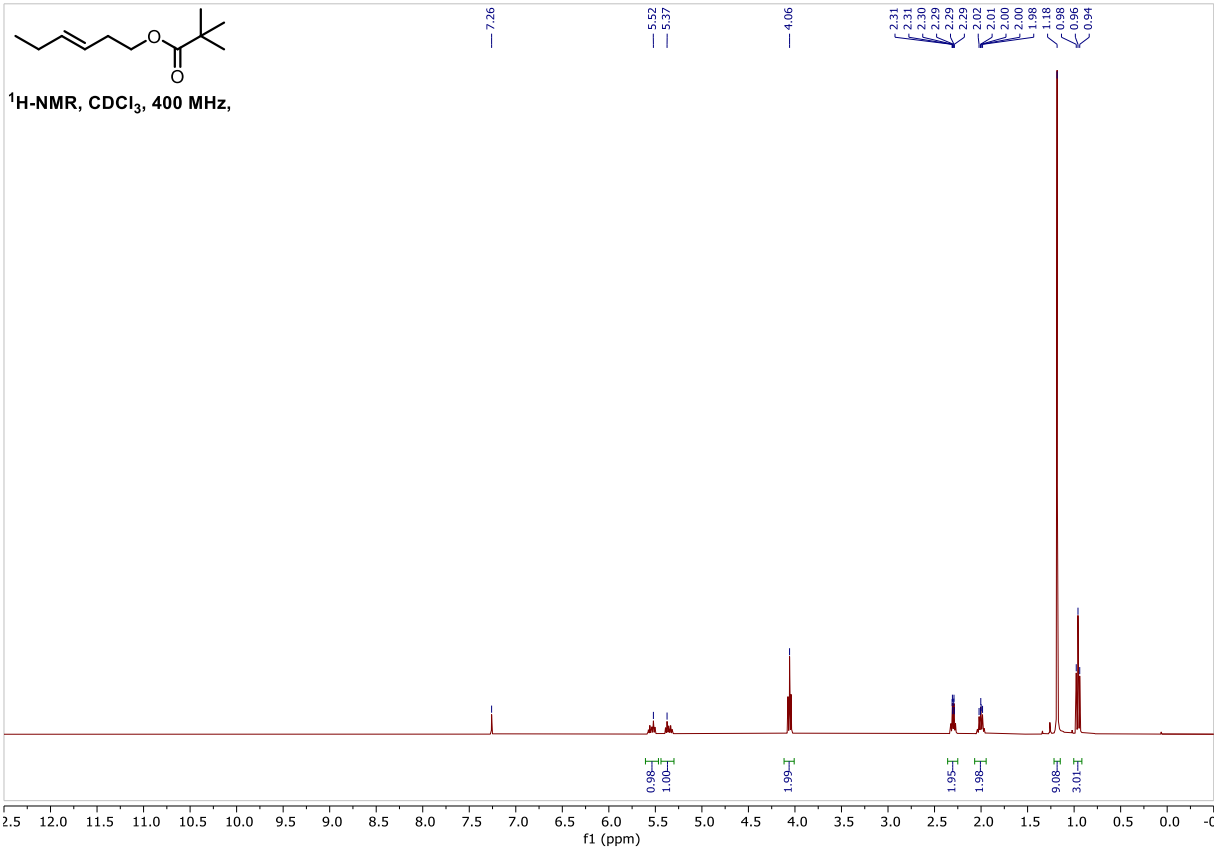


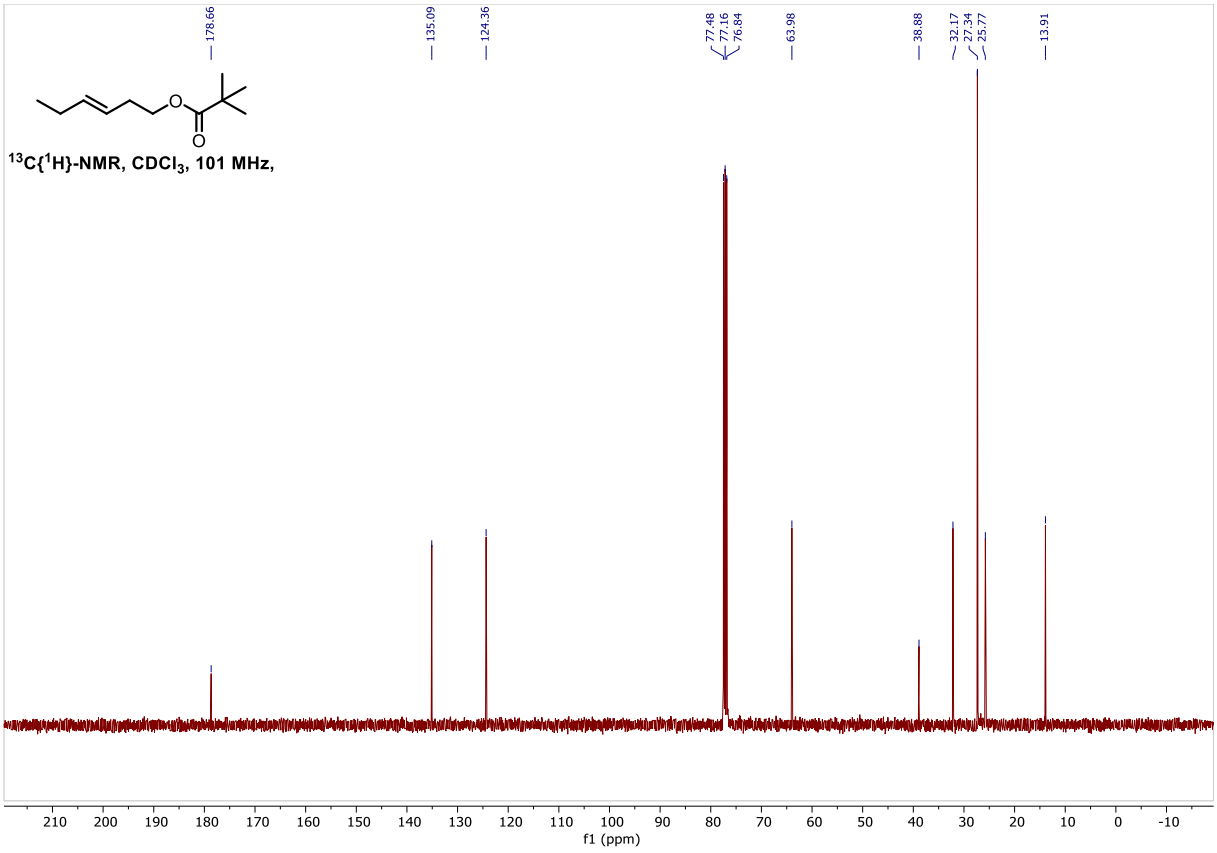
Methyl 2-bromo-3-chlorobenzoate (**2.2l**)



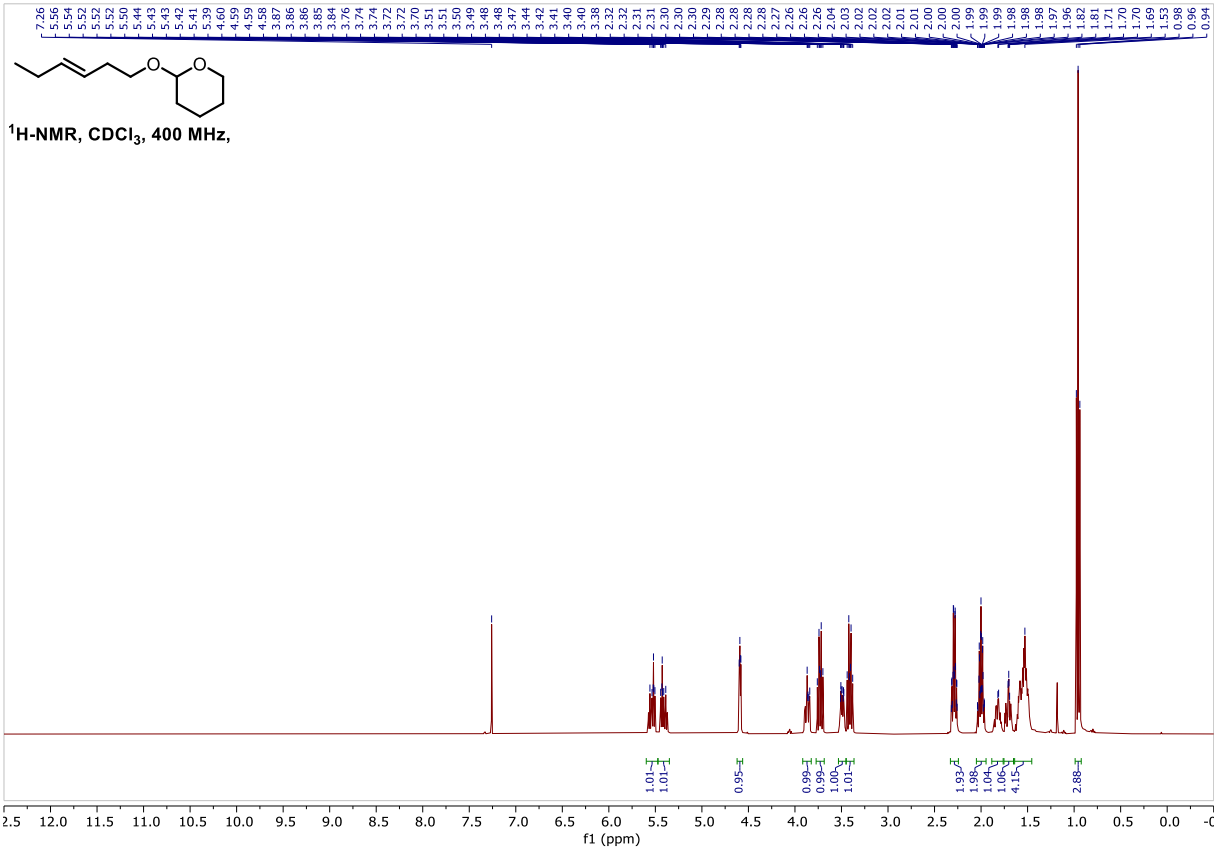


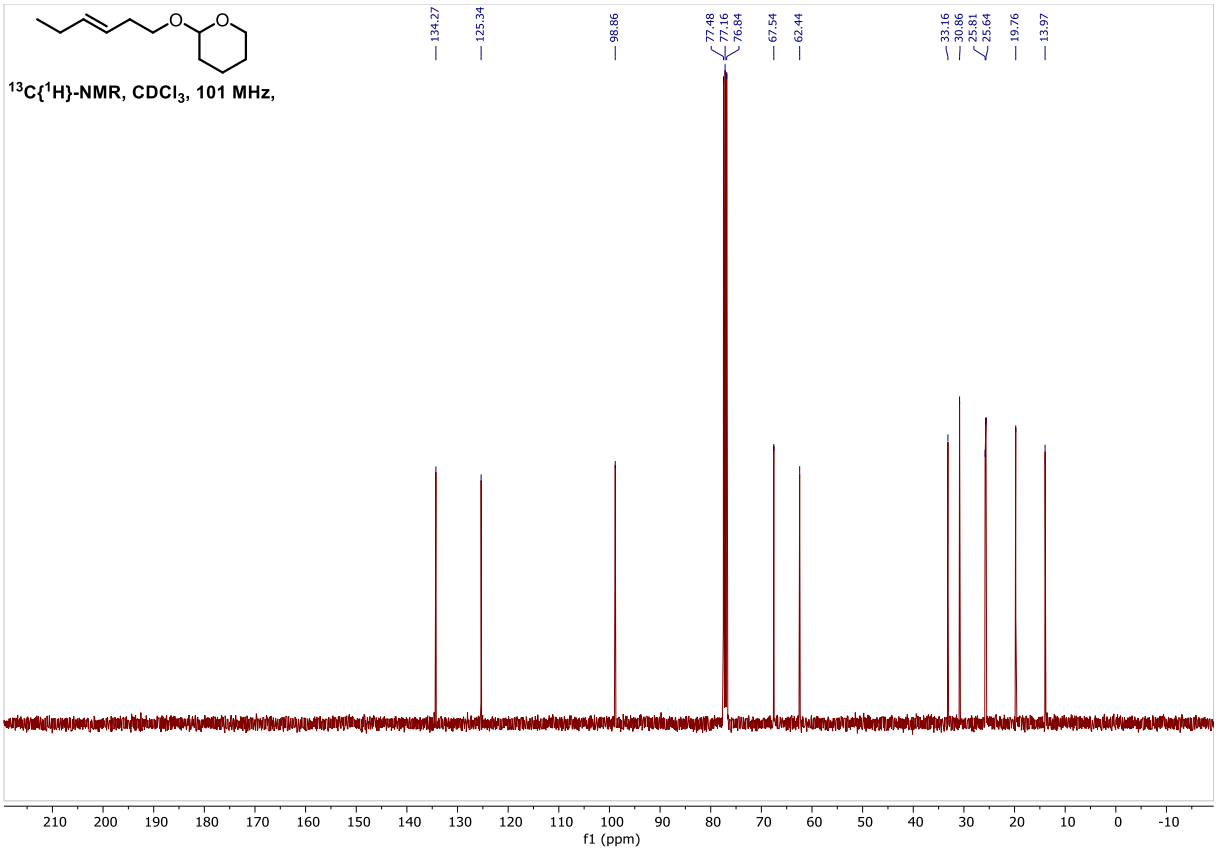
(*E*)-hex-3-en-1-yl pivalate (**2.1c**)



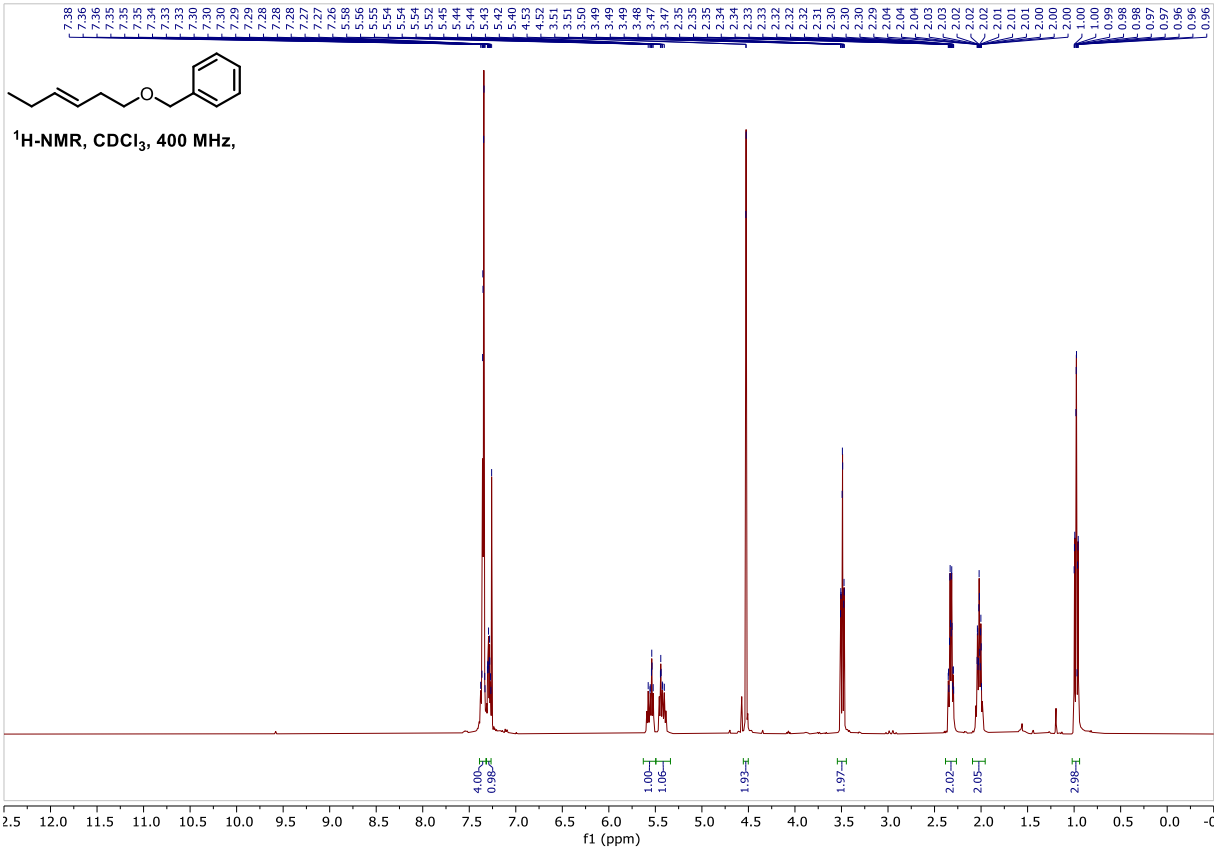


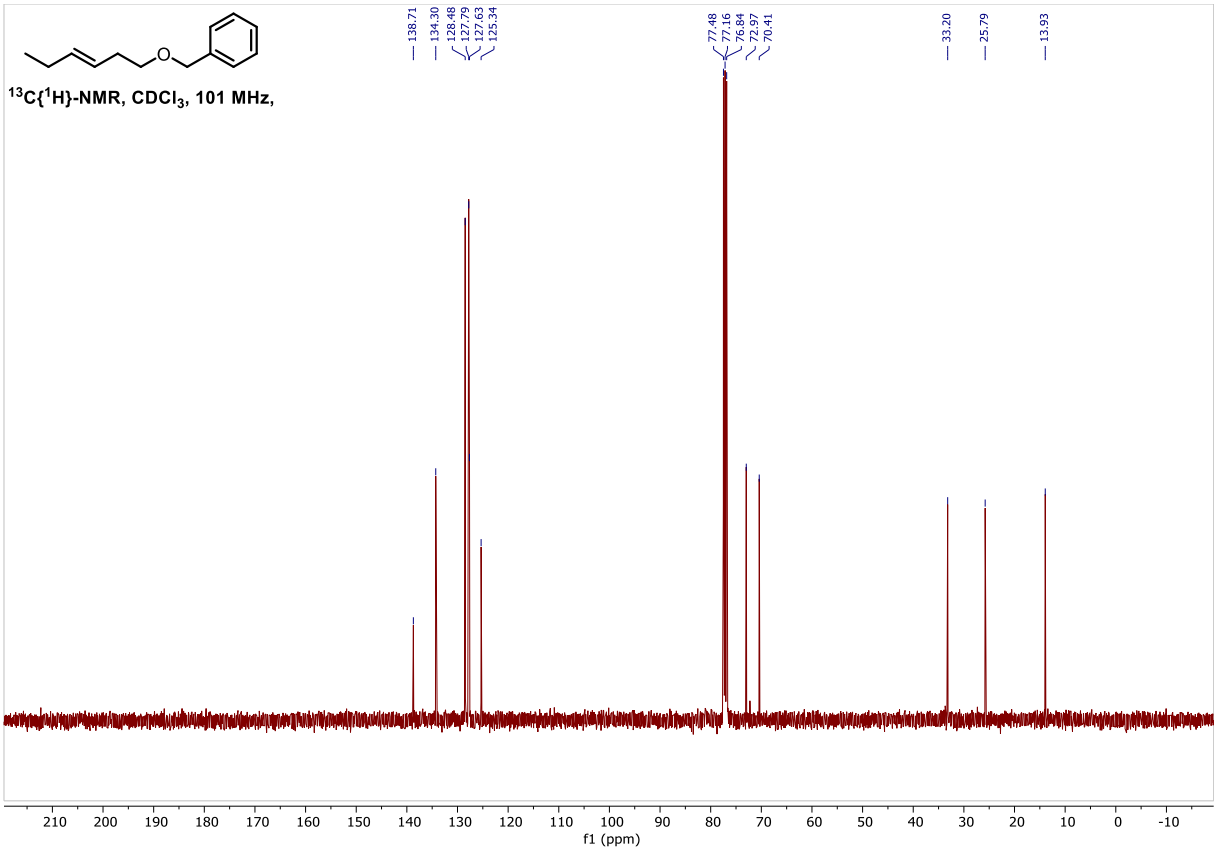
(*E*)-2-(hex-3-en-1-yloxy)tetrahydro-2H-pyran (**2.1d**)



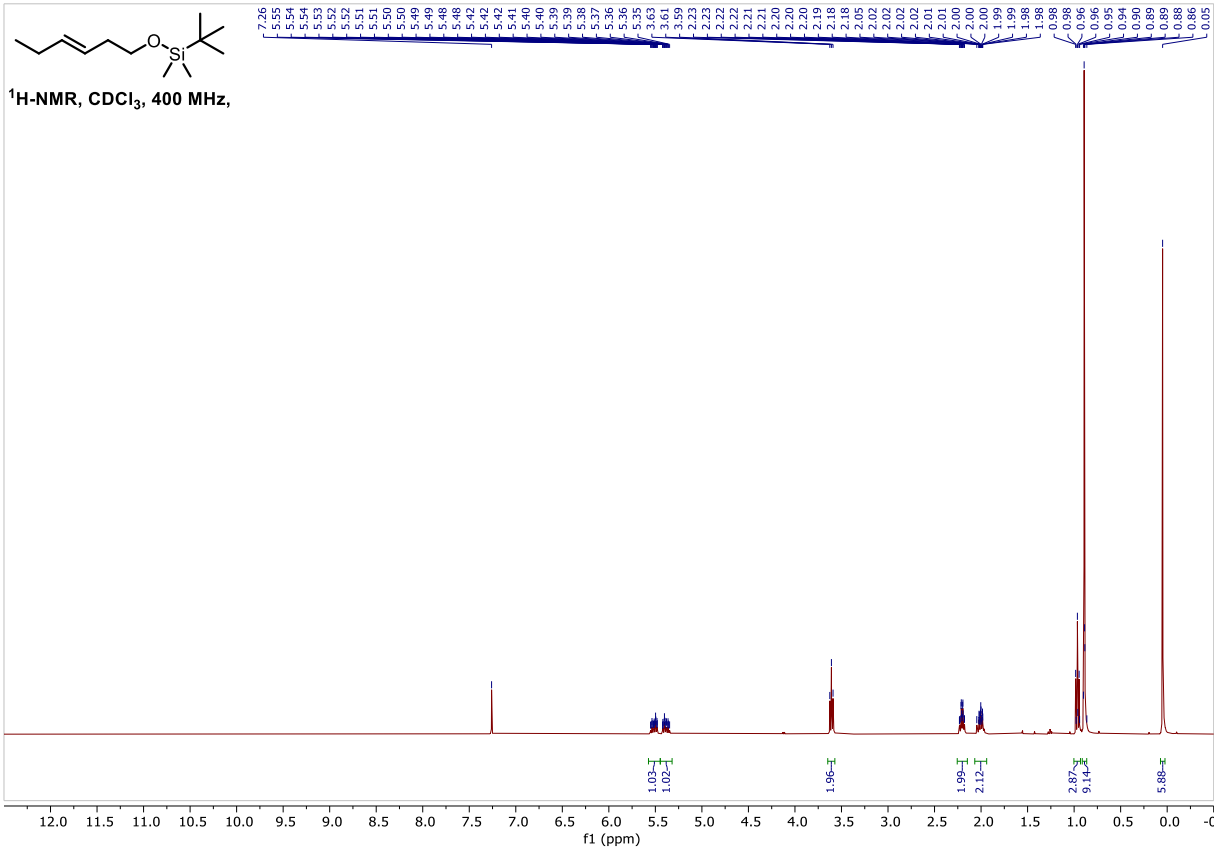


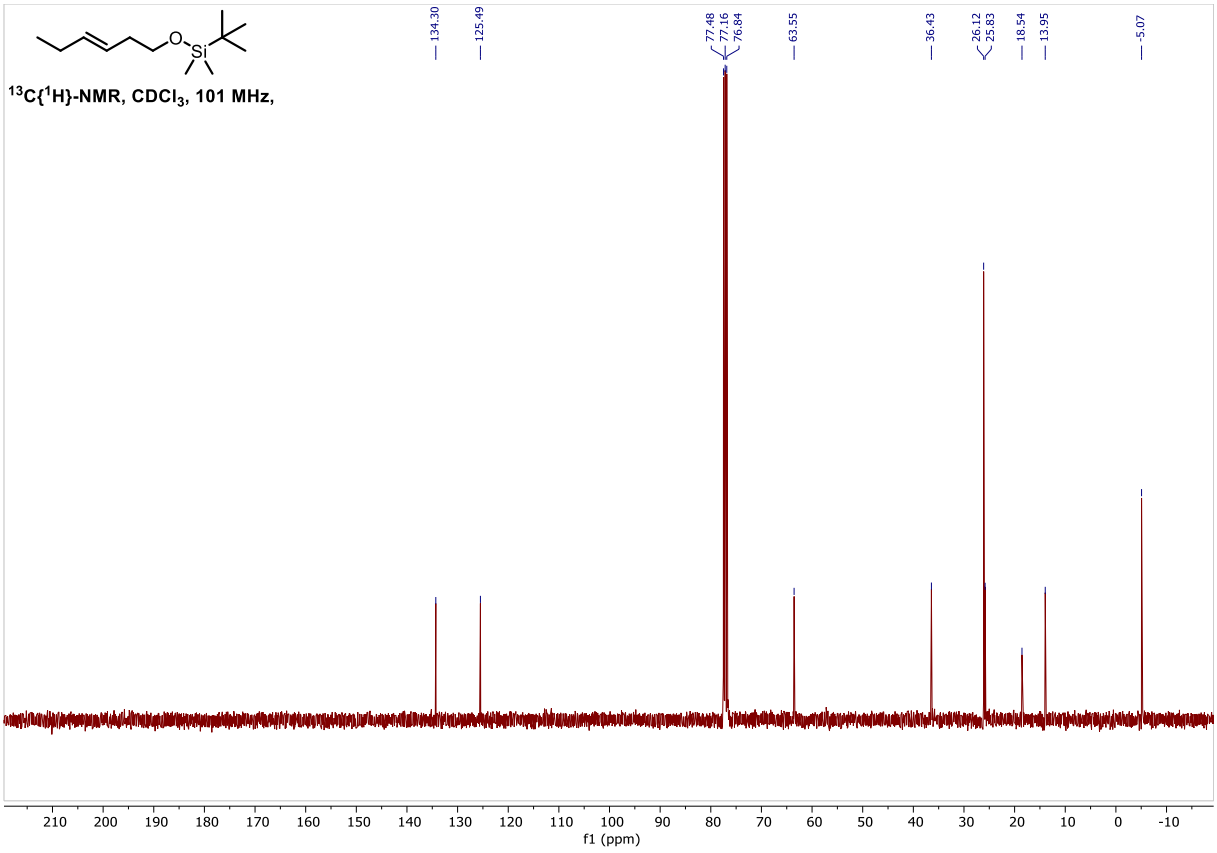
(*E*)-((hex-3-en-1-yloxy)methyl)benzene (**2.1e**)



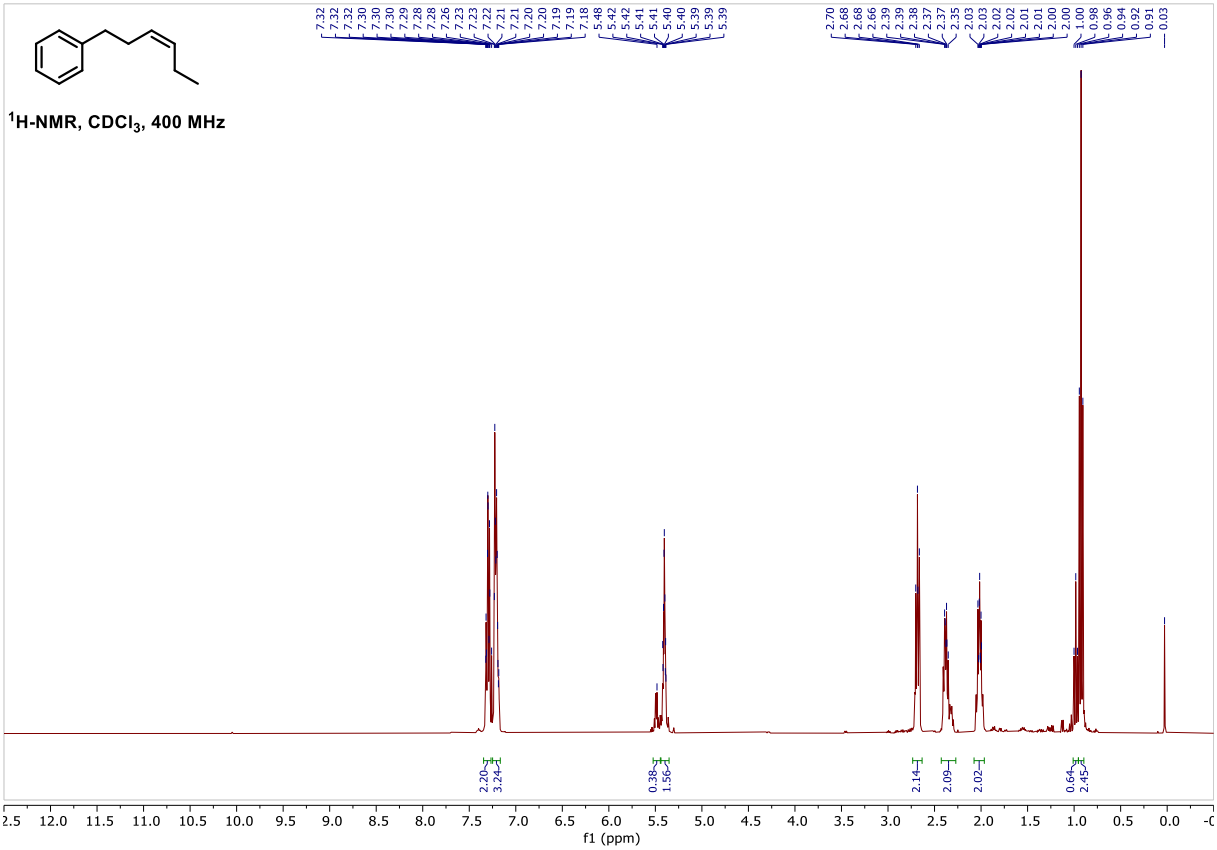


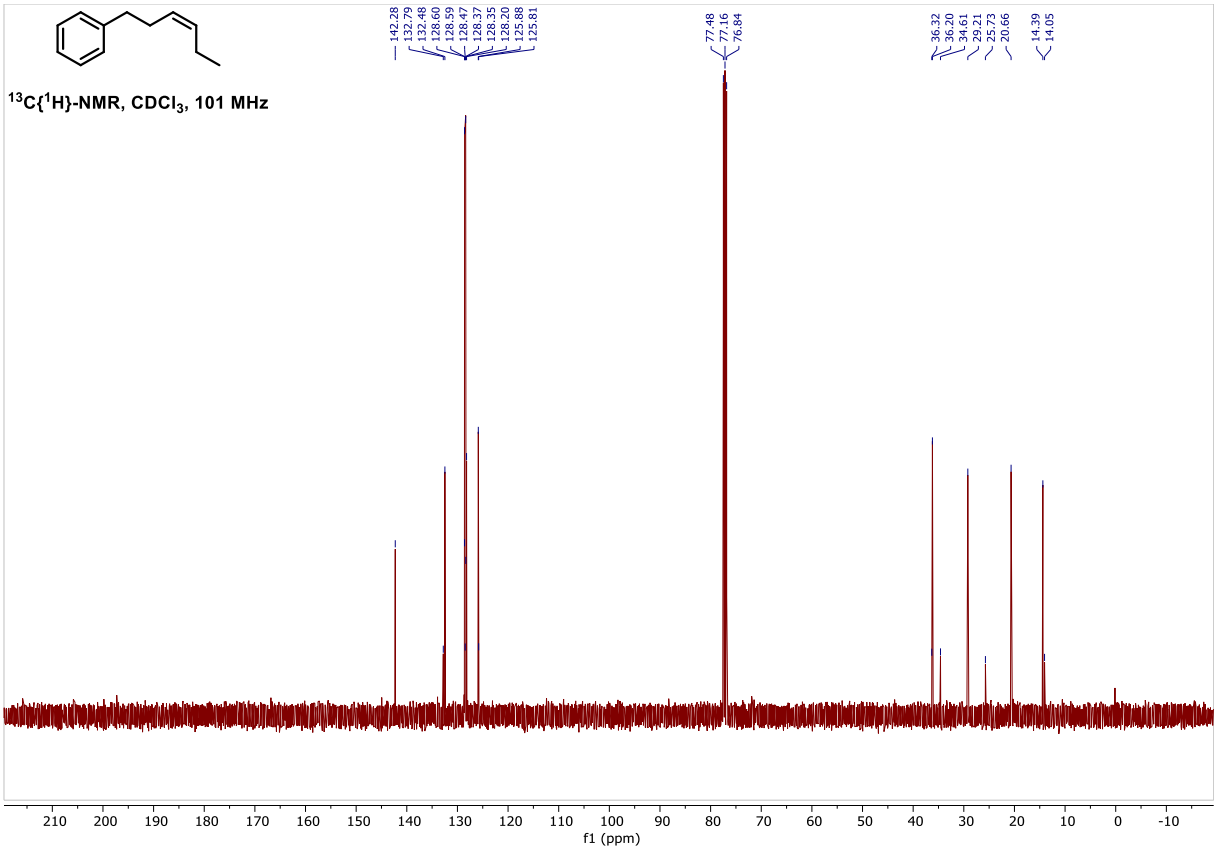
(*E*)-*tert*-Butyl(hex-3-en-1-yloxy)dimethylsilane (**2.1f**)



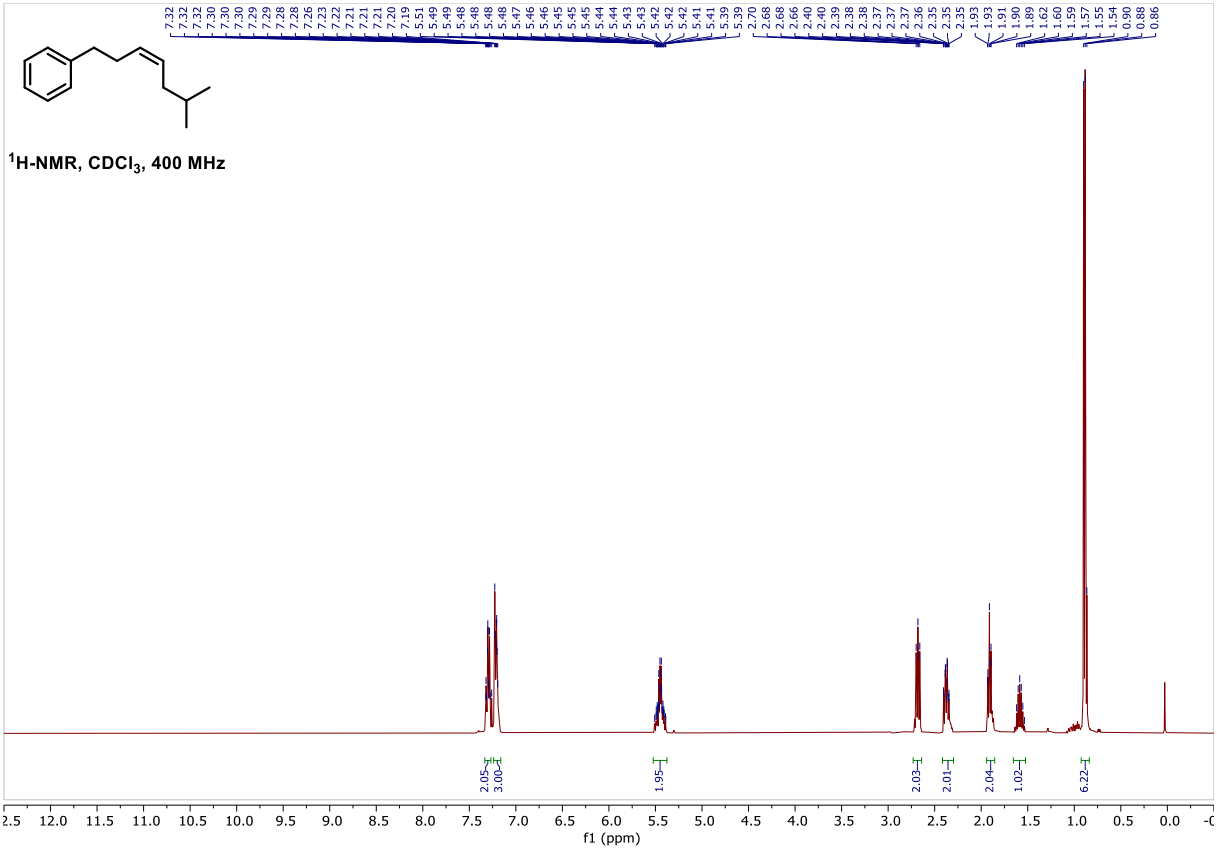


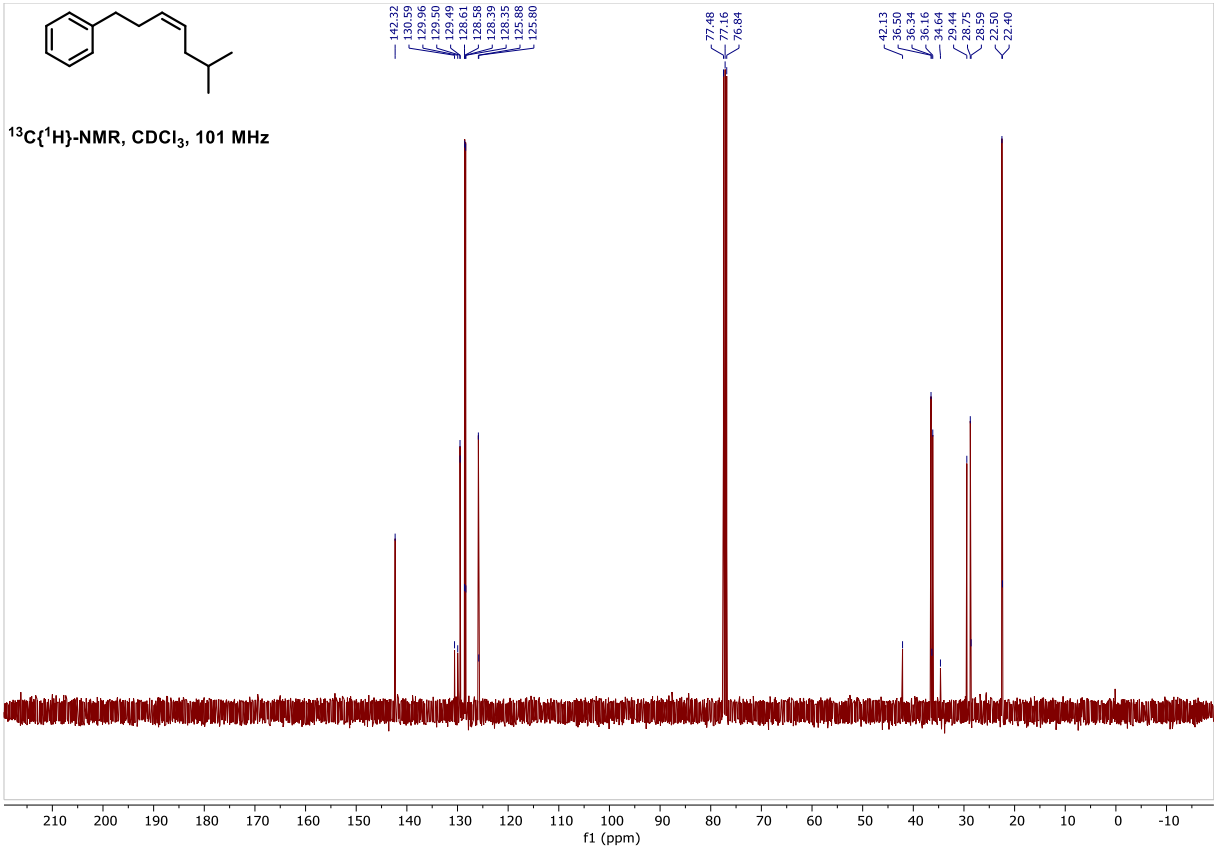
(*Z*)-Hex-3-en-1-ylbenzene (1a)



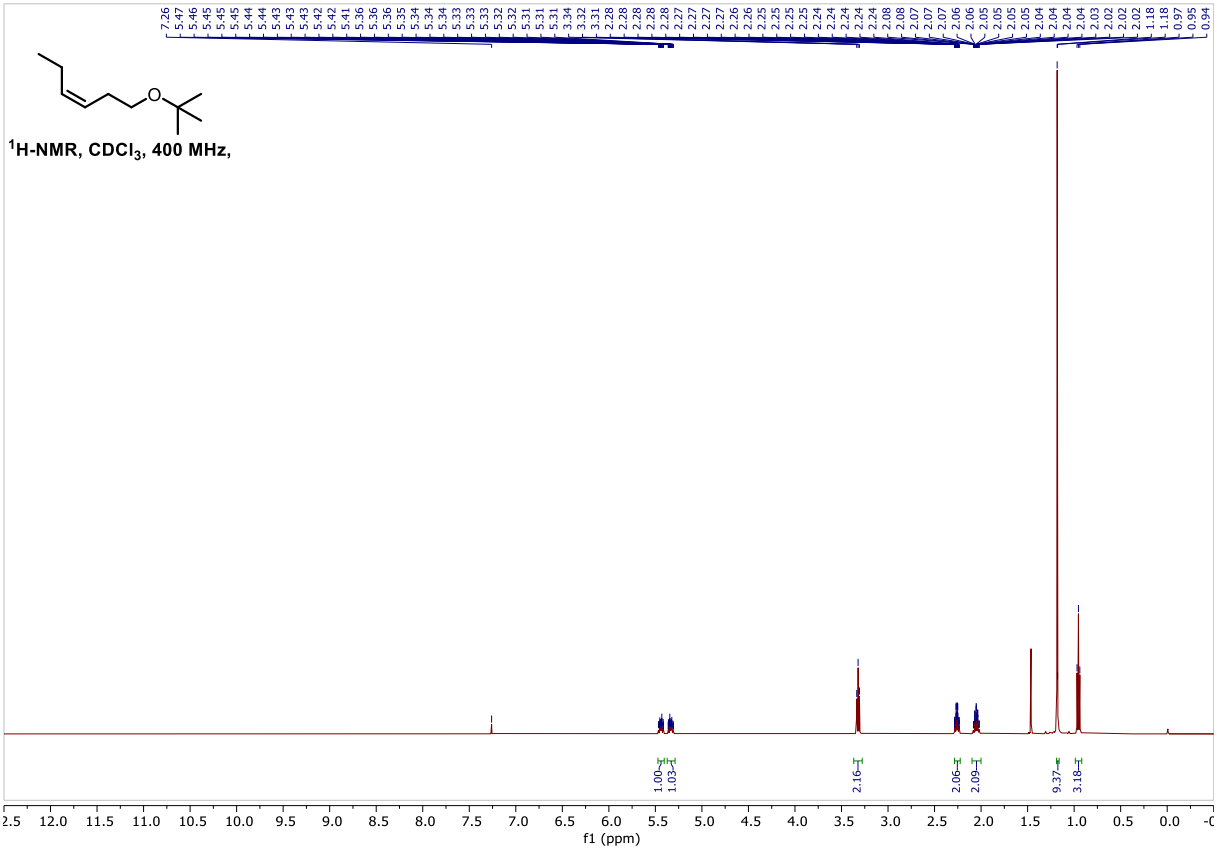


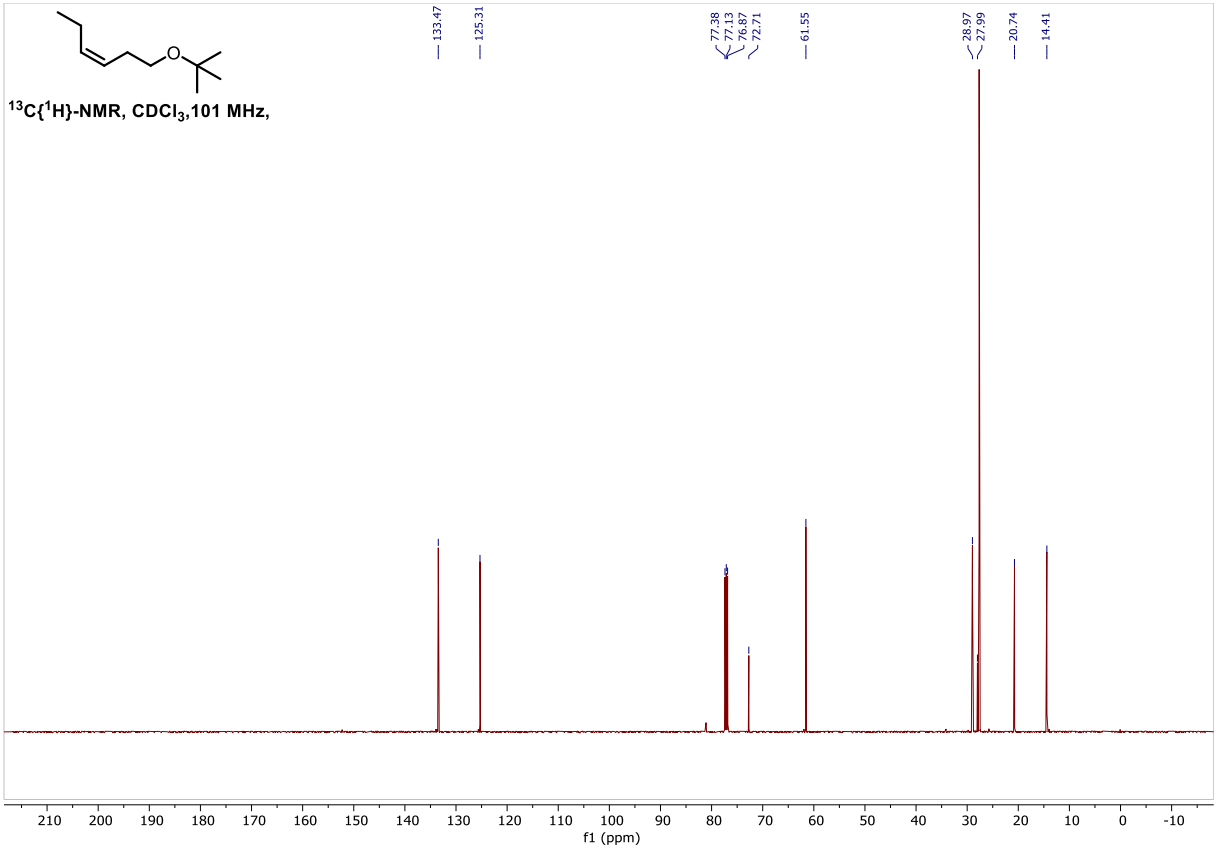
(*Z*)-(6-Methylhept-3-en-1-yl)benzene (1b)



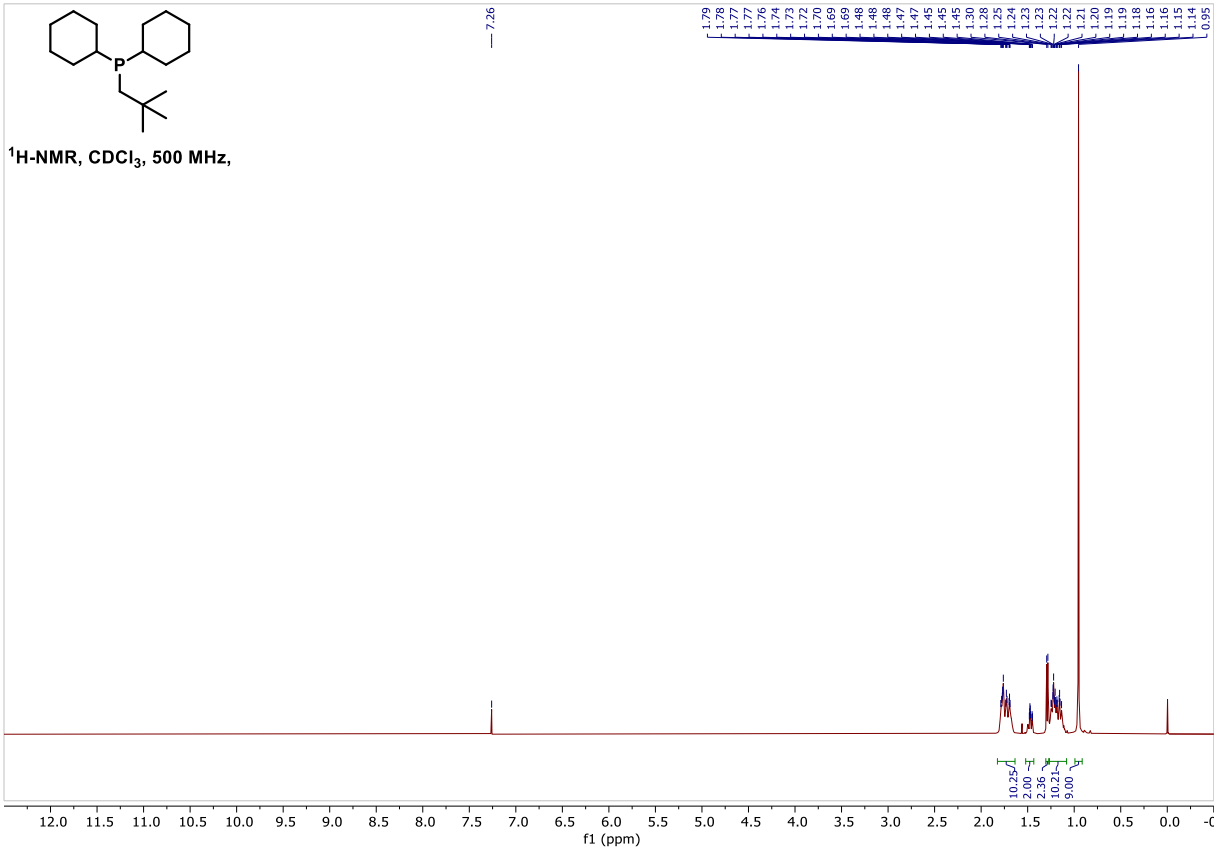


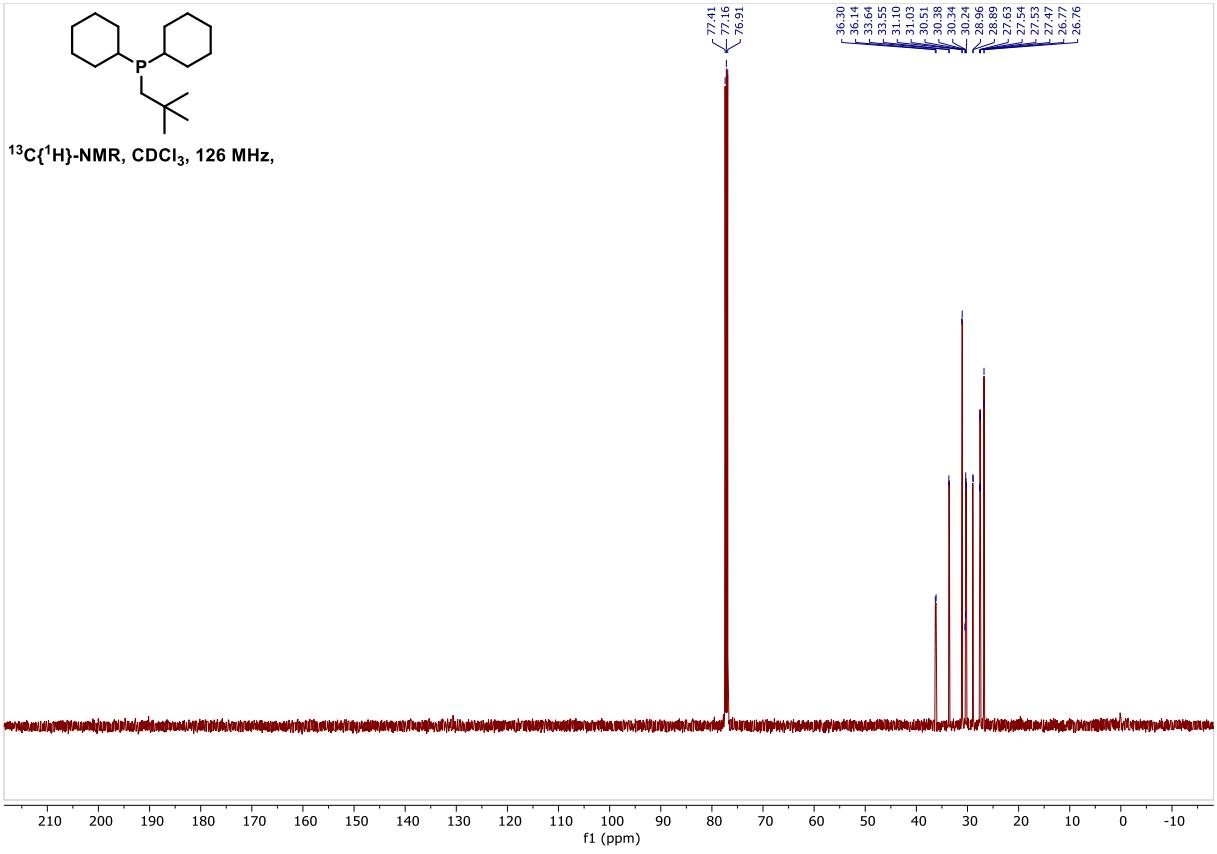
(*Z*)-1-(*tert*-Butoxy)hex-3-ene (**2.1j**)



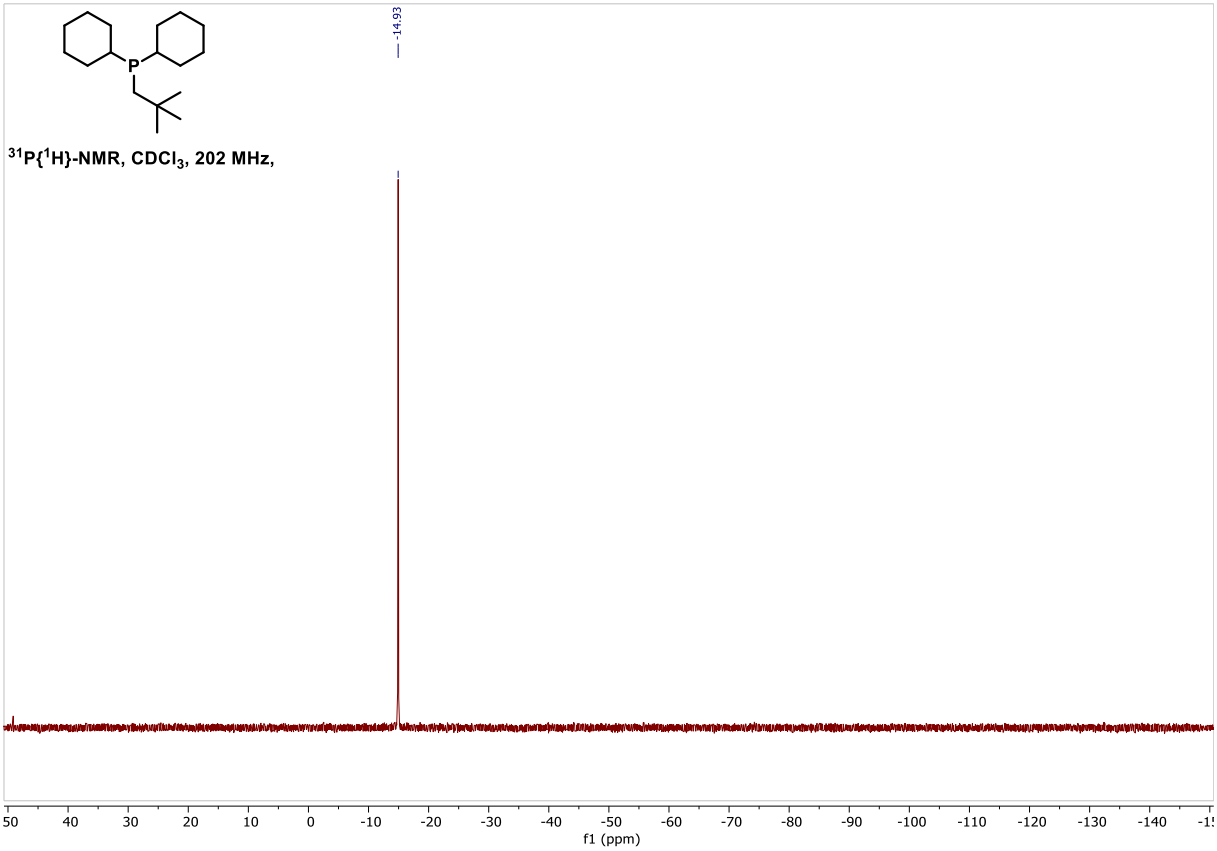


Dicyclohexyl(neopentyl)phosphine (**L2.36**)



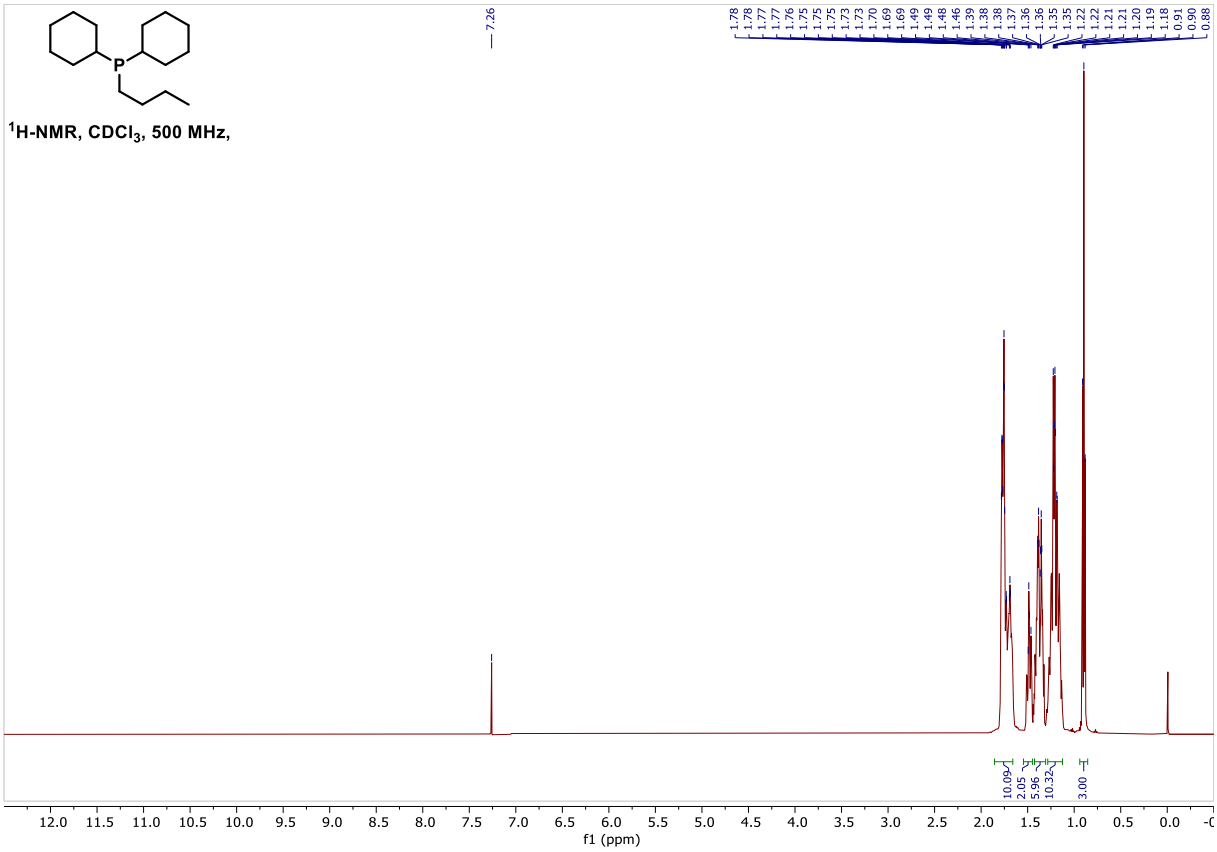


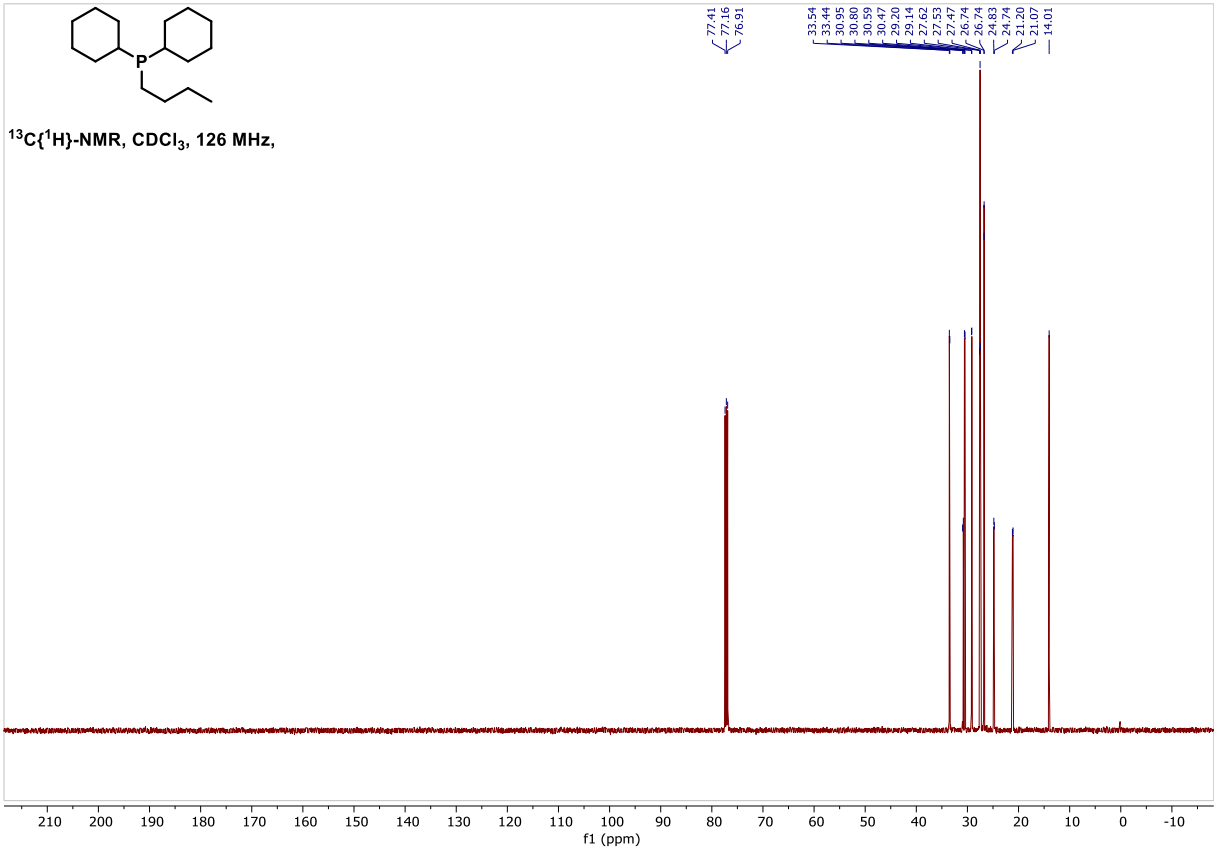
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

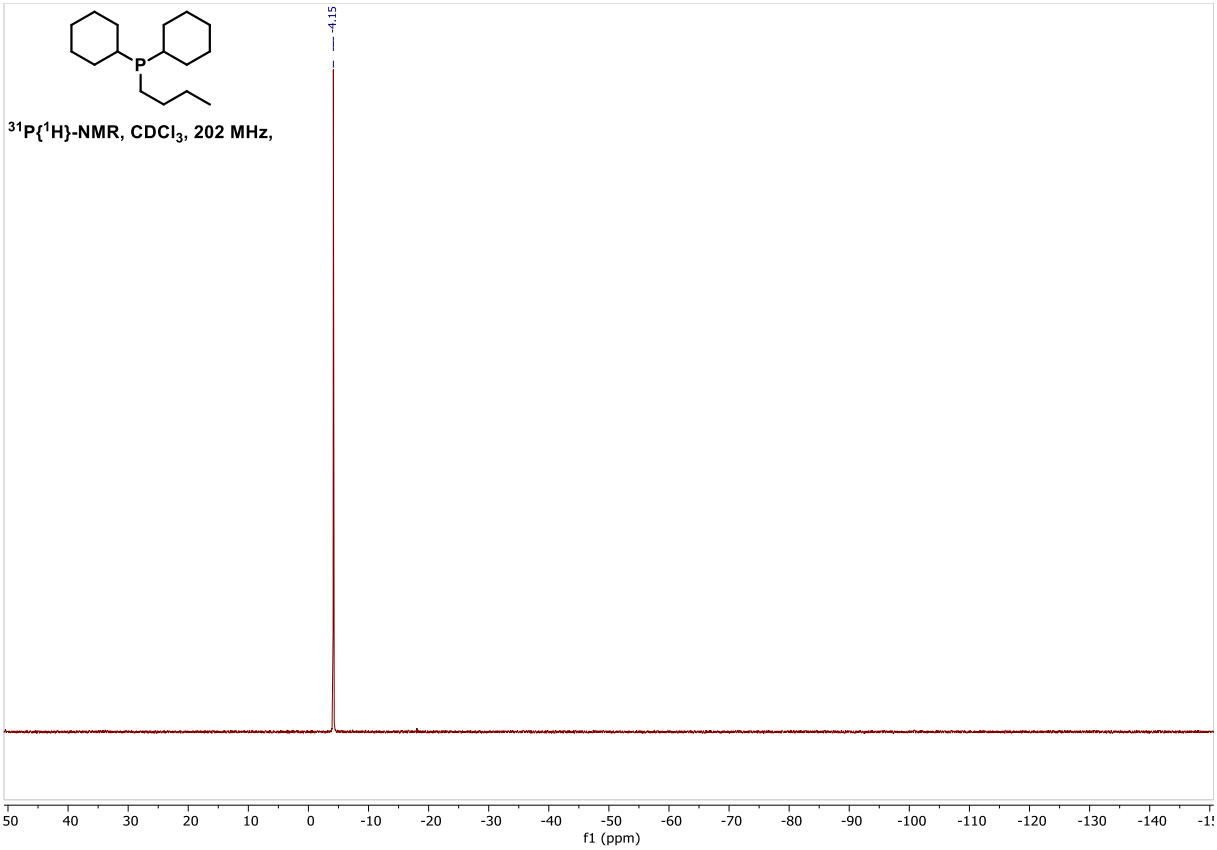


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 202 MHz,

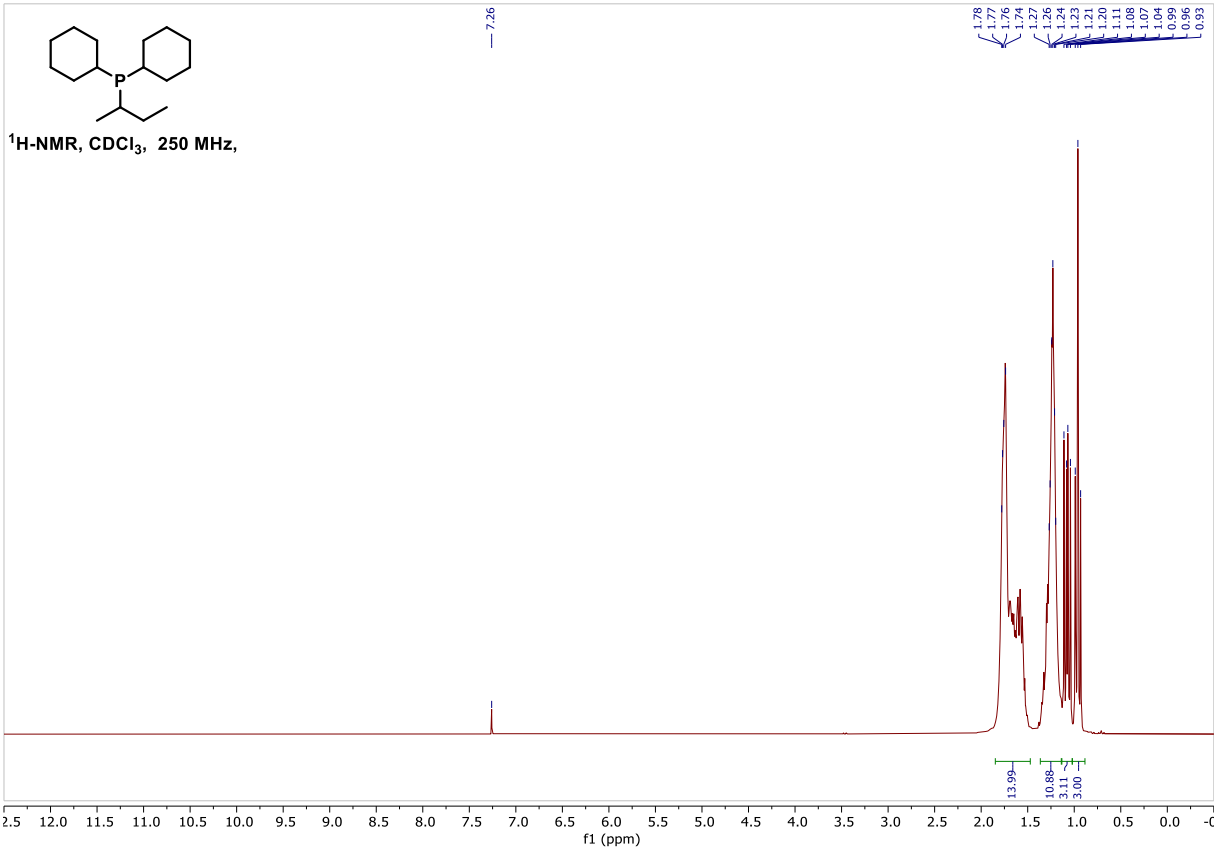
Butyldicyclohexylphosphine (**L2.37**)

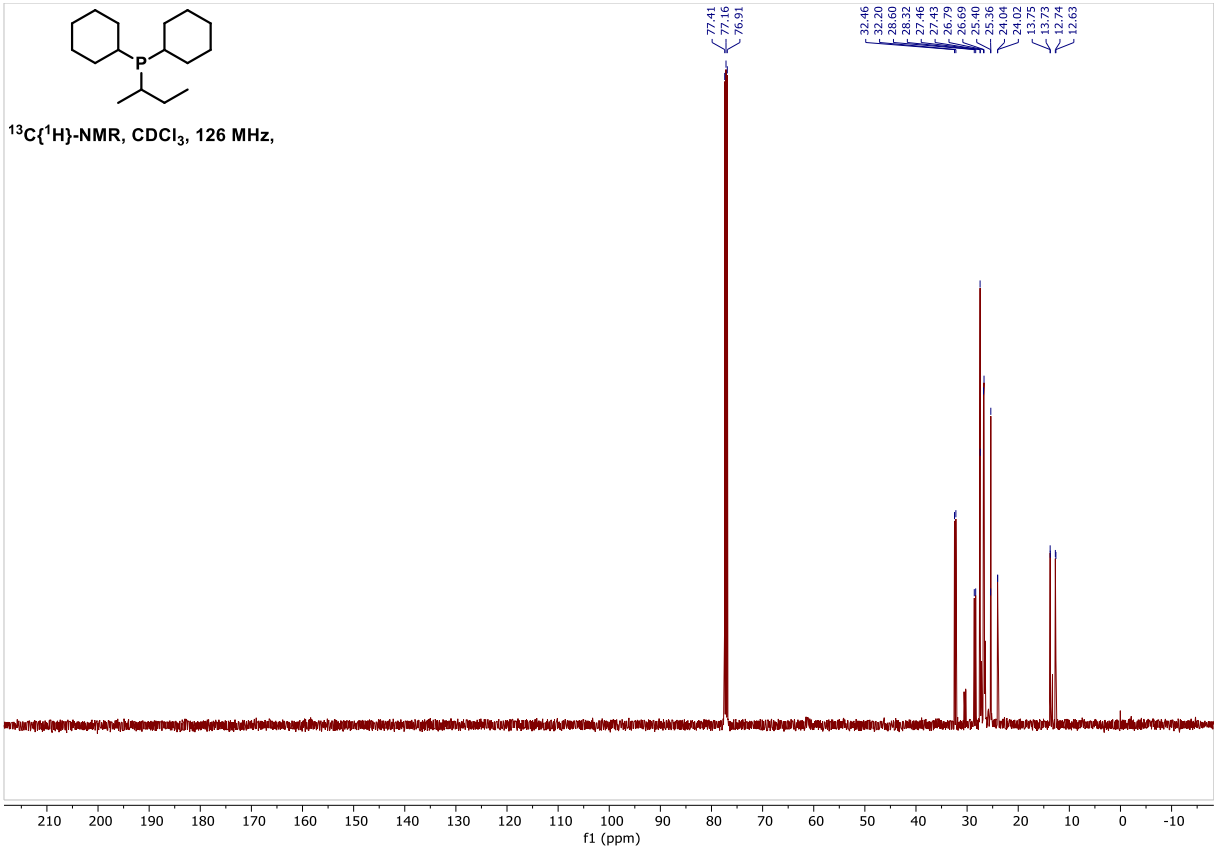




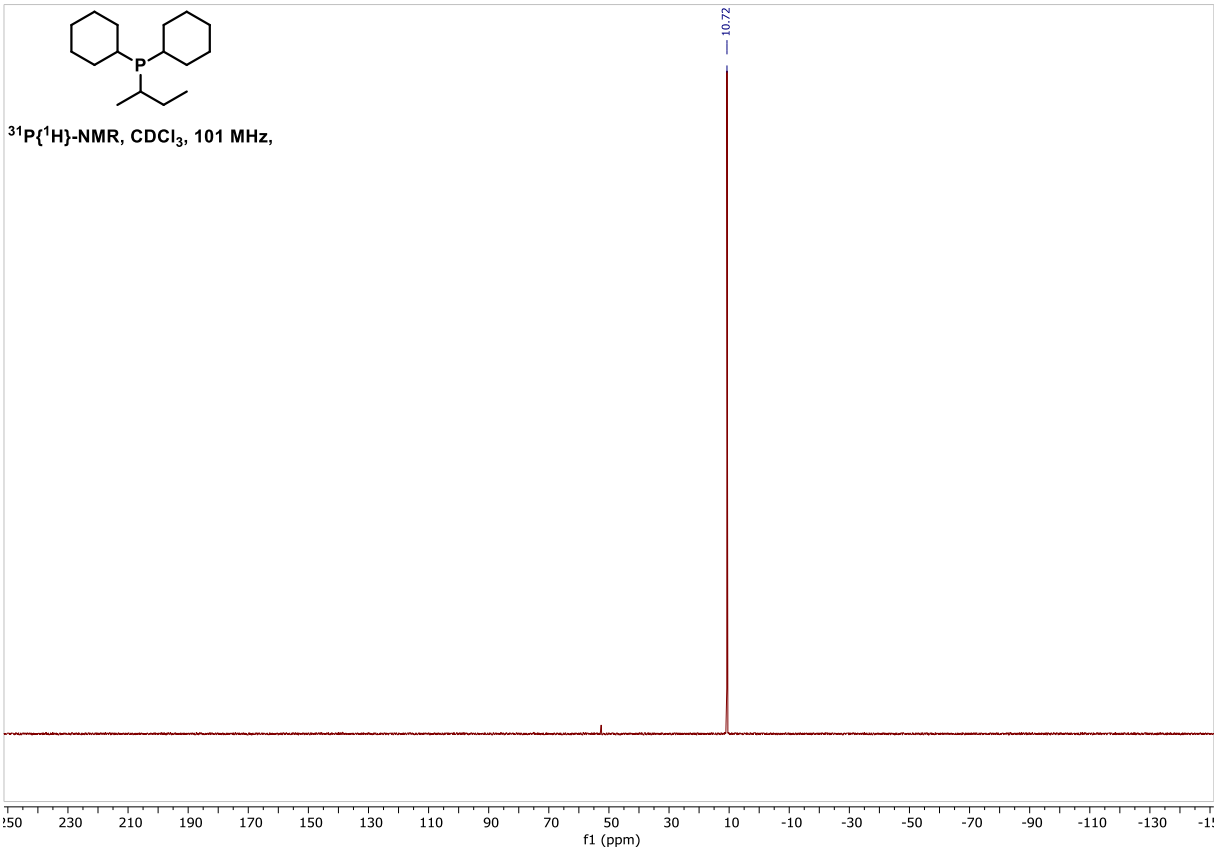


sec-Butyldicyclohexylphosphine (**L2.38**)



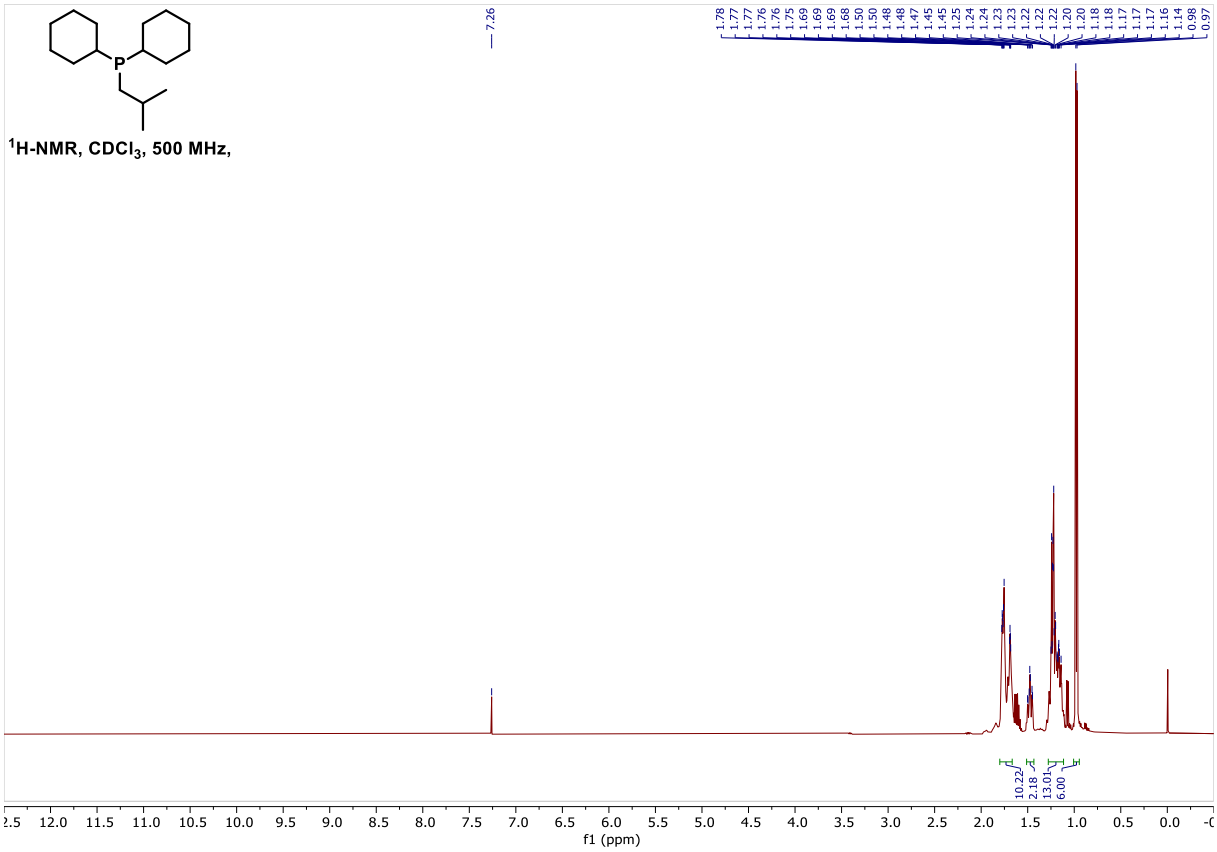


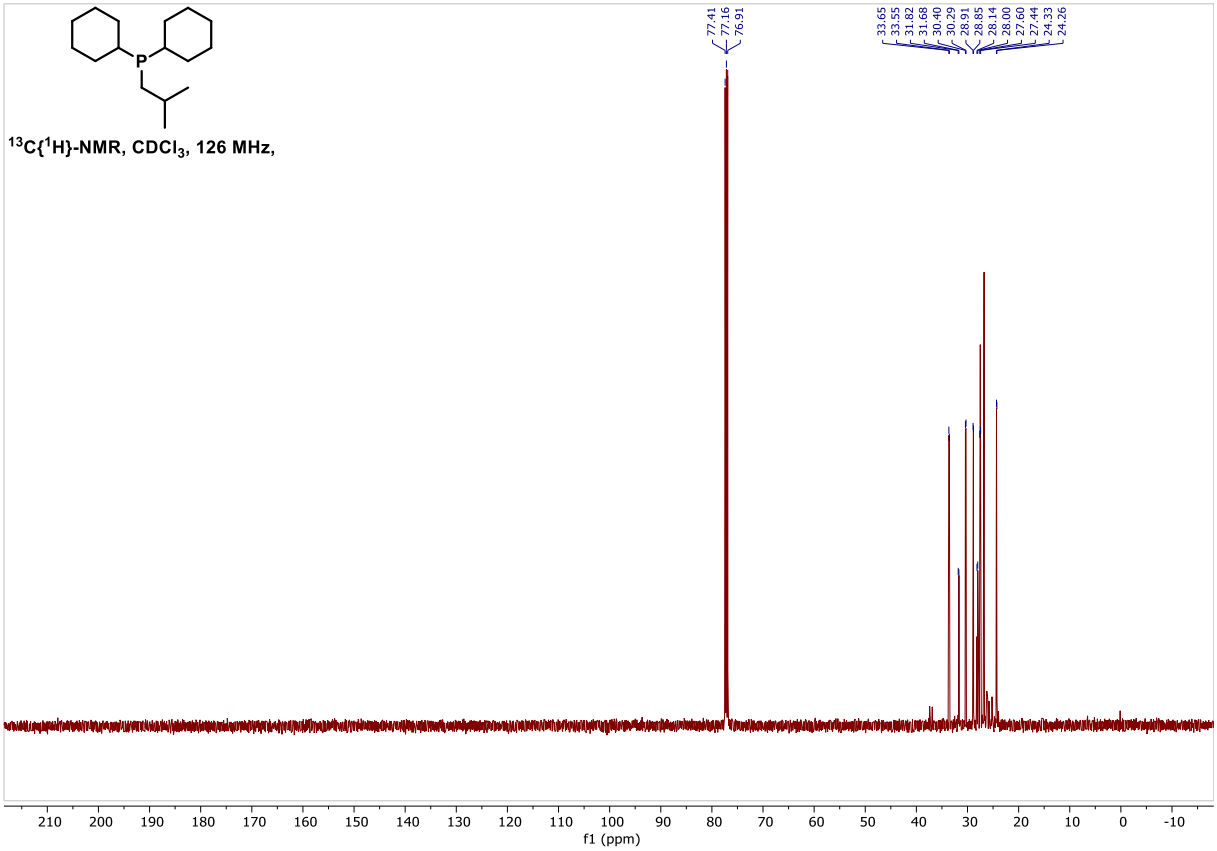
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

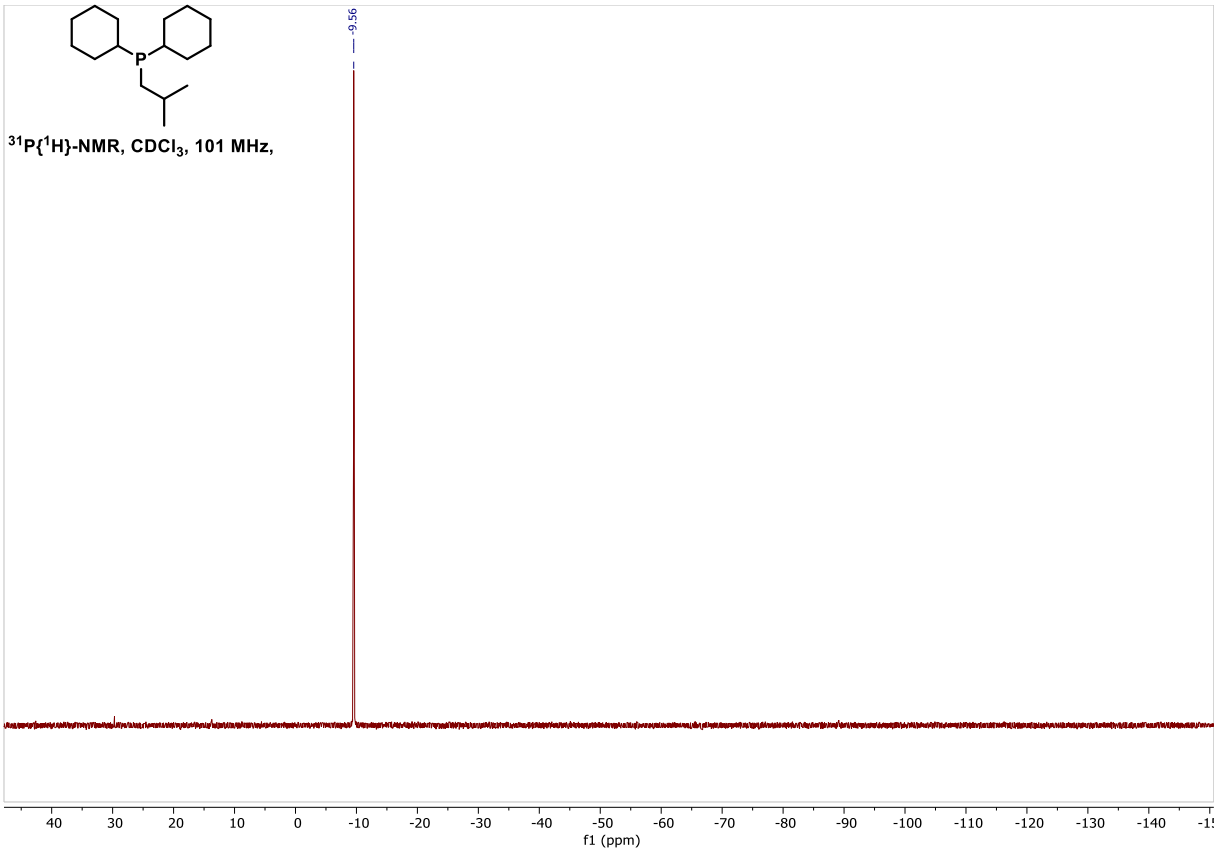


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 101 MHz,

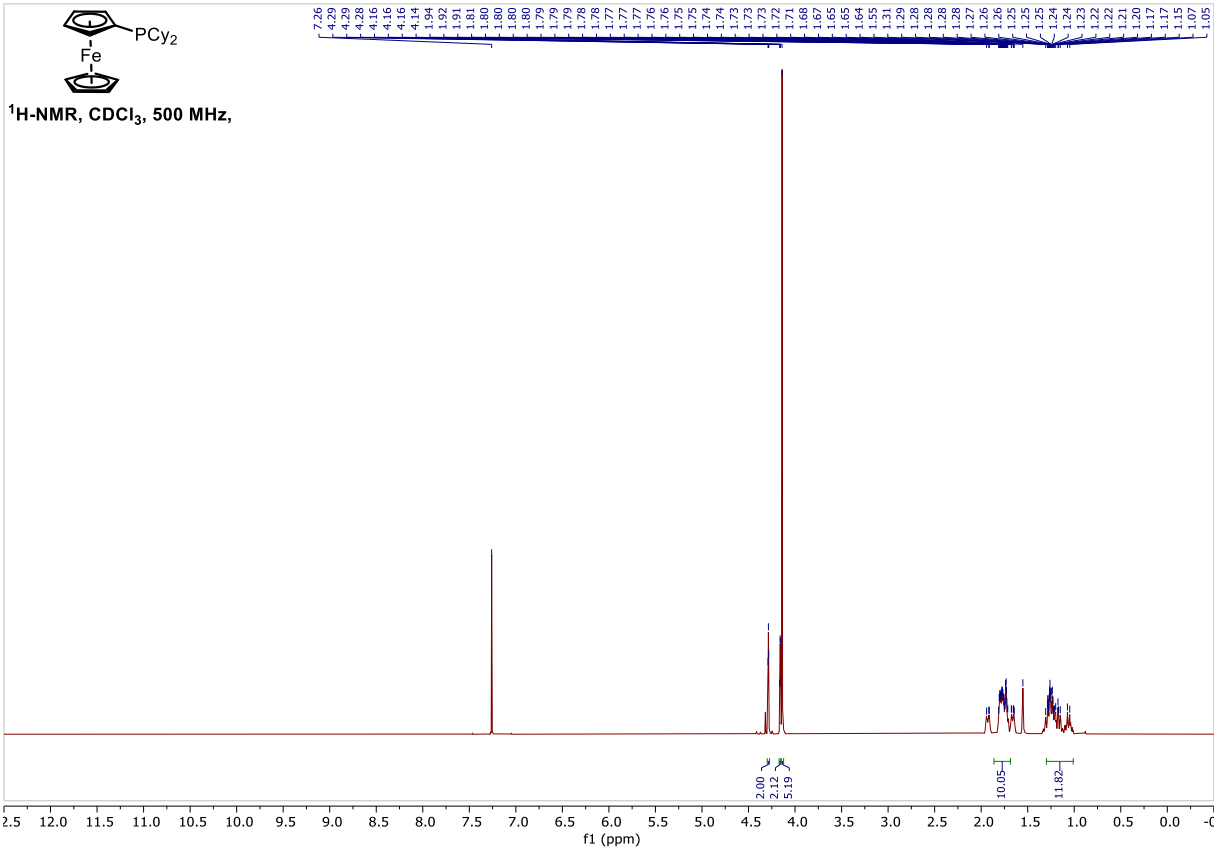
Dicyclohexyl(isobutyl)phosphine (**L2.39**)

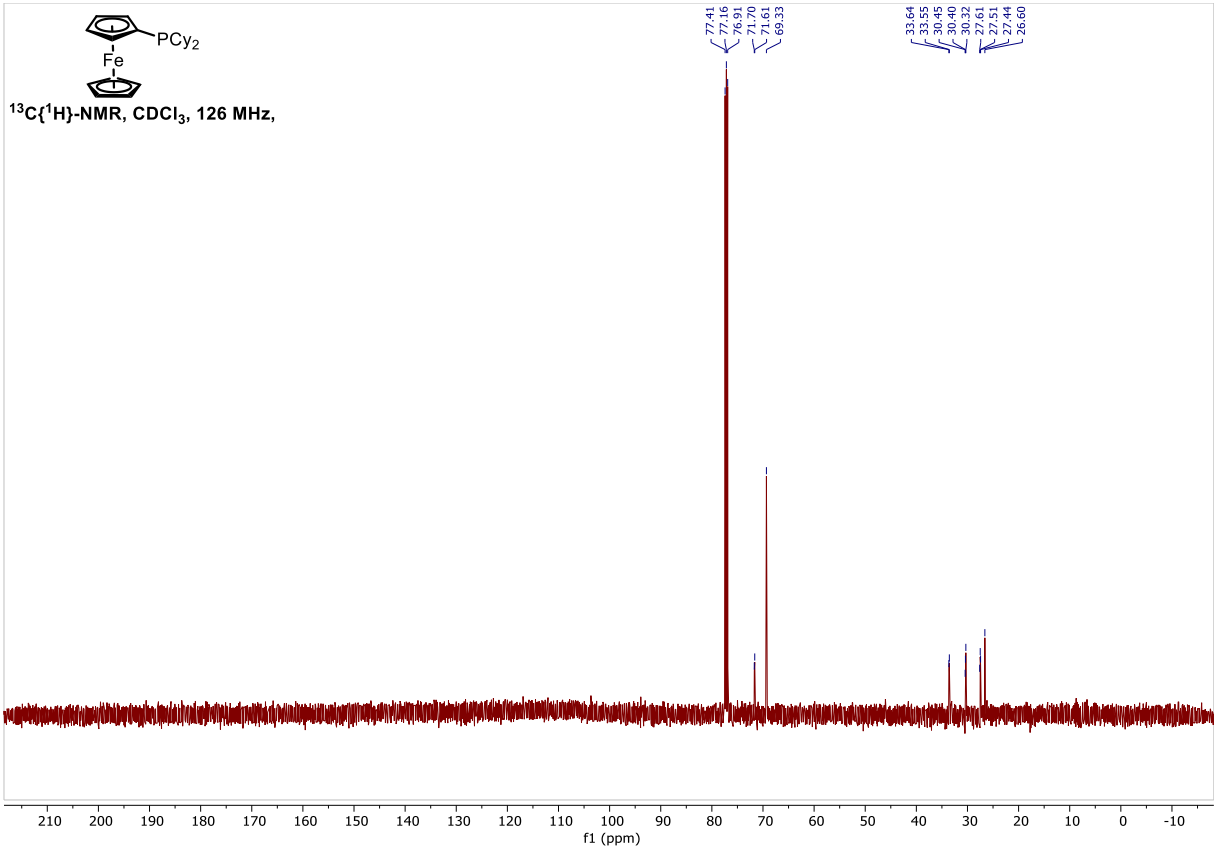


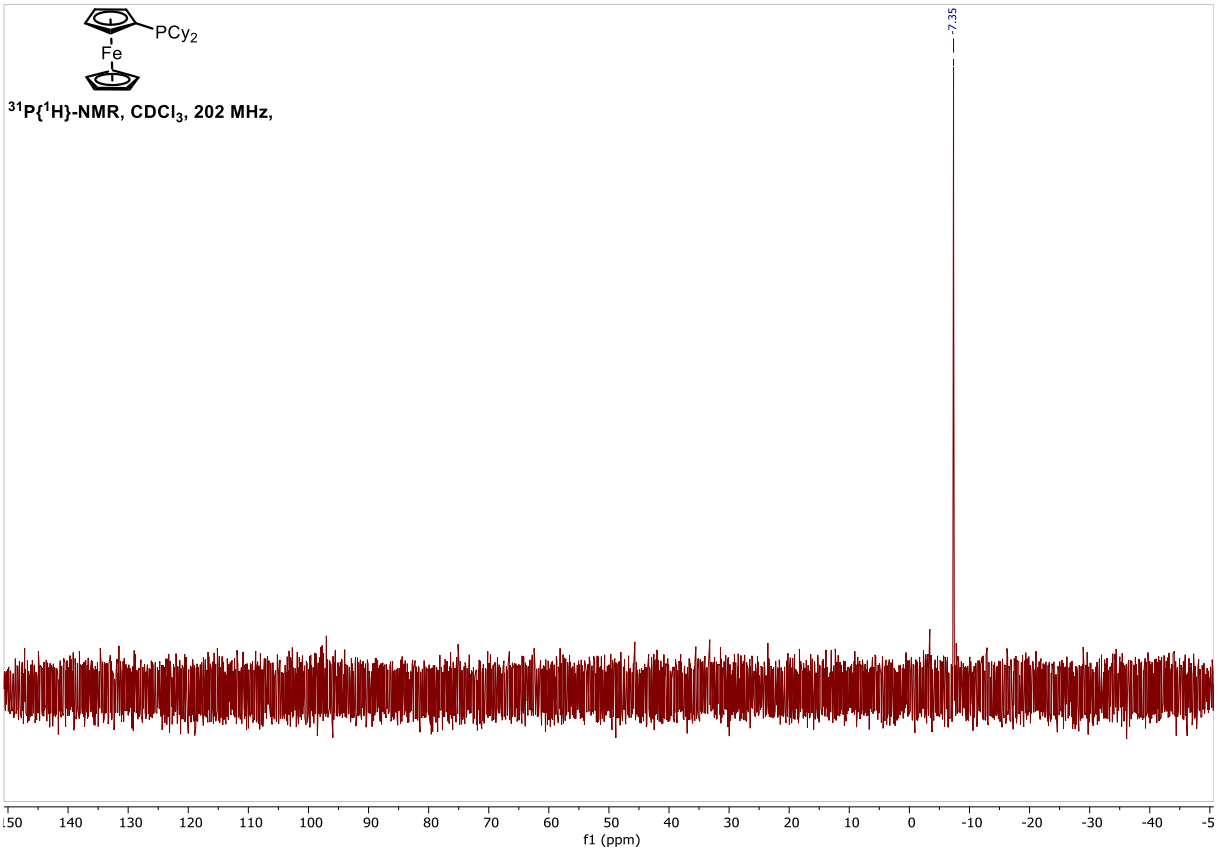




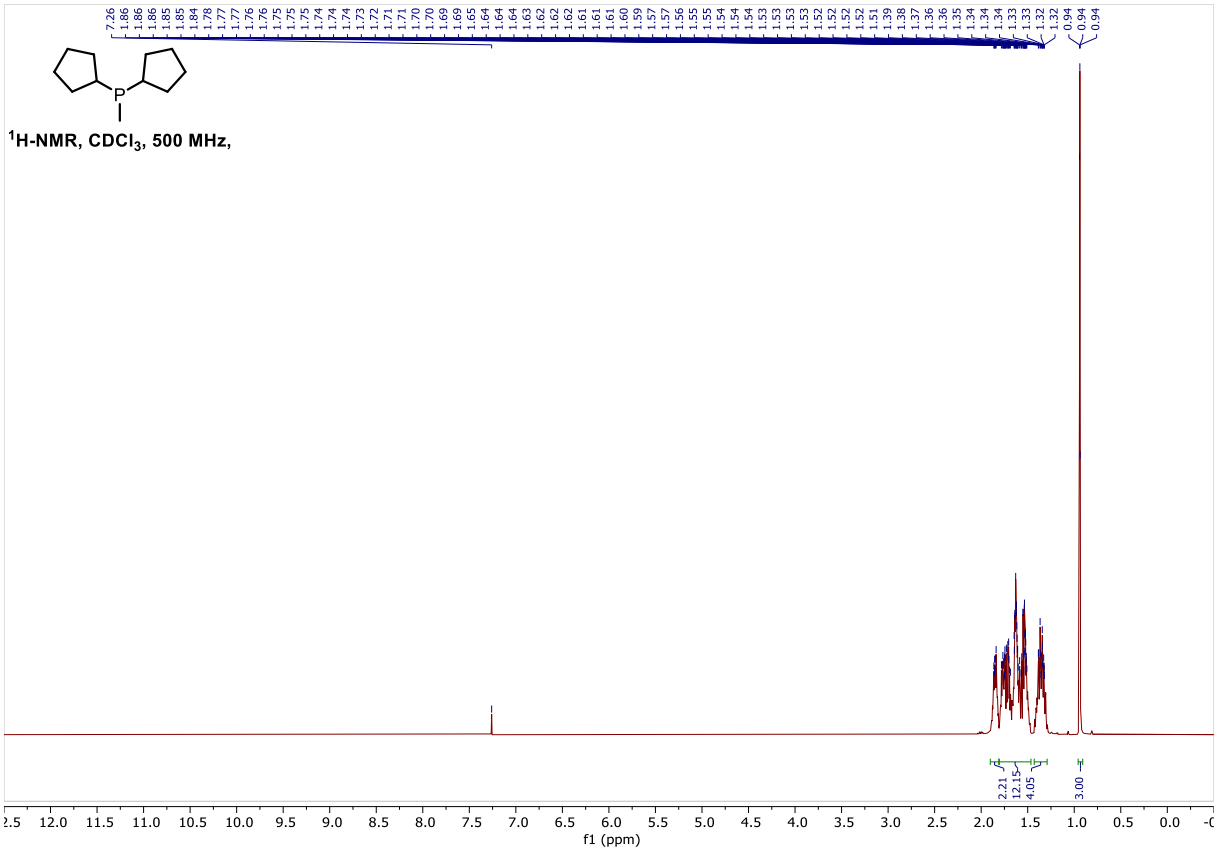
Dicyclohexylferrocenylphosphine (**L2.40**)

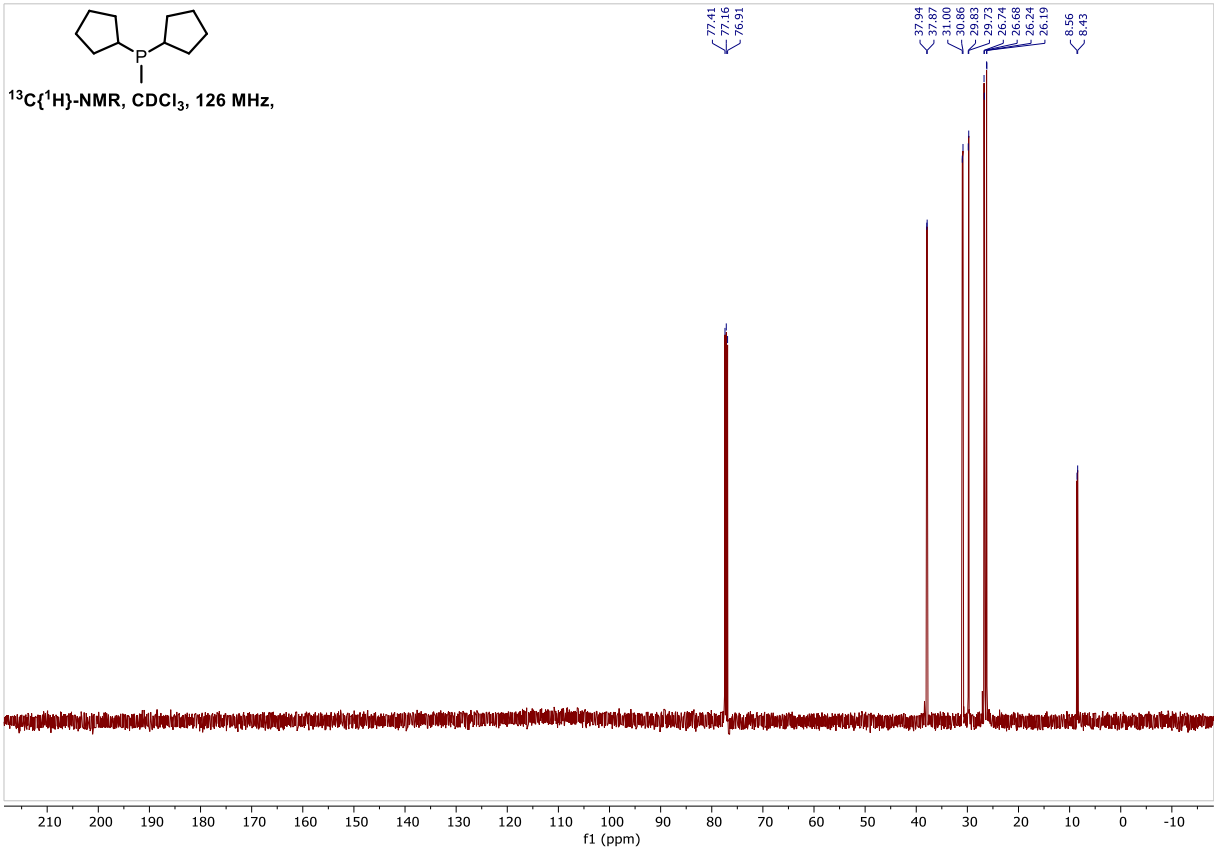


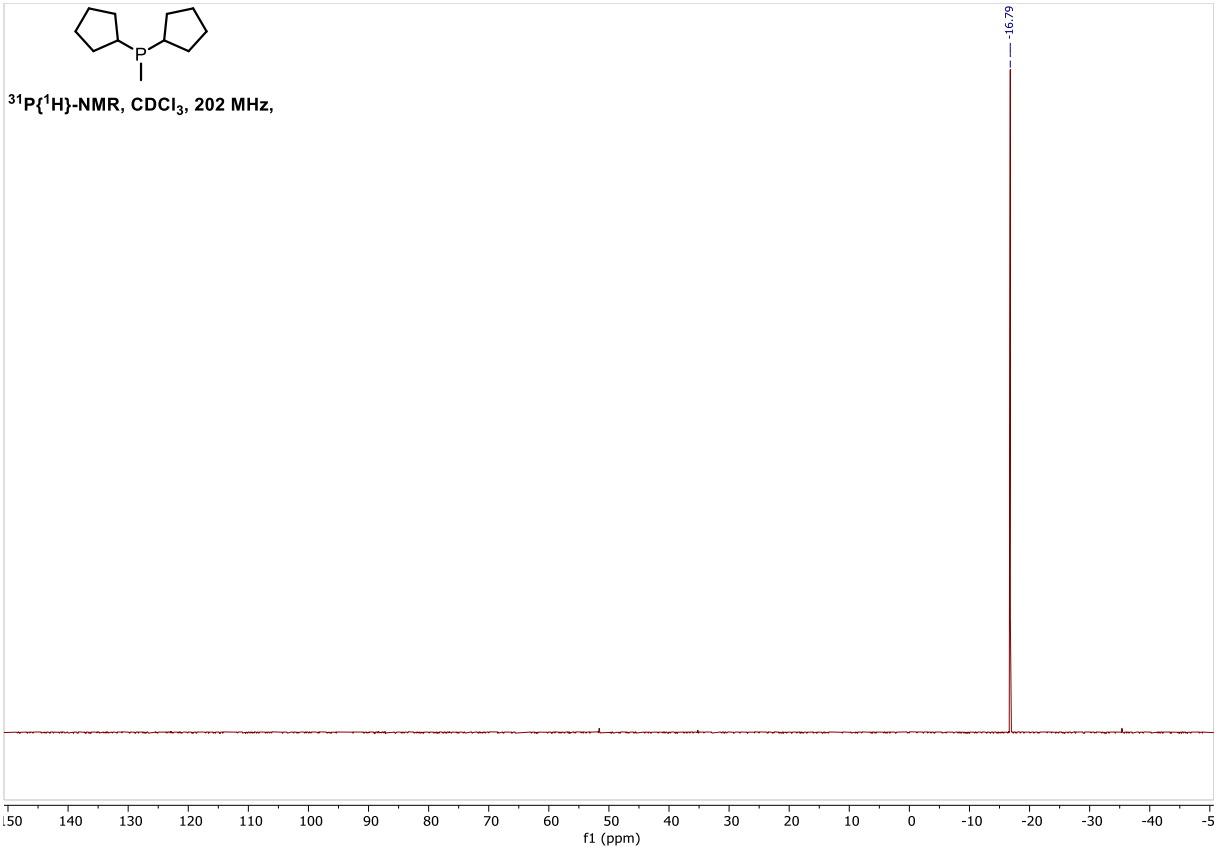

PCy2
Fe
13C{1H}-NMR, CDCl3, 126 MHz,
77.41
77.16
76.91
71.70
71.61
69.33
33.64
33.55
30.45
30.40
30.32
27.61
27.51
27.44
26.60
f1 (ppm)


PCy2
Fe
31P{1H}-NMR, CDCl3, 202 MHz,
-7.35
f1 (ppm)

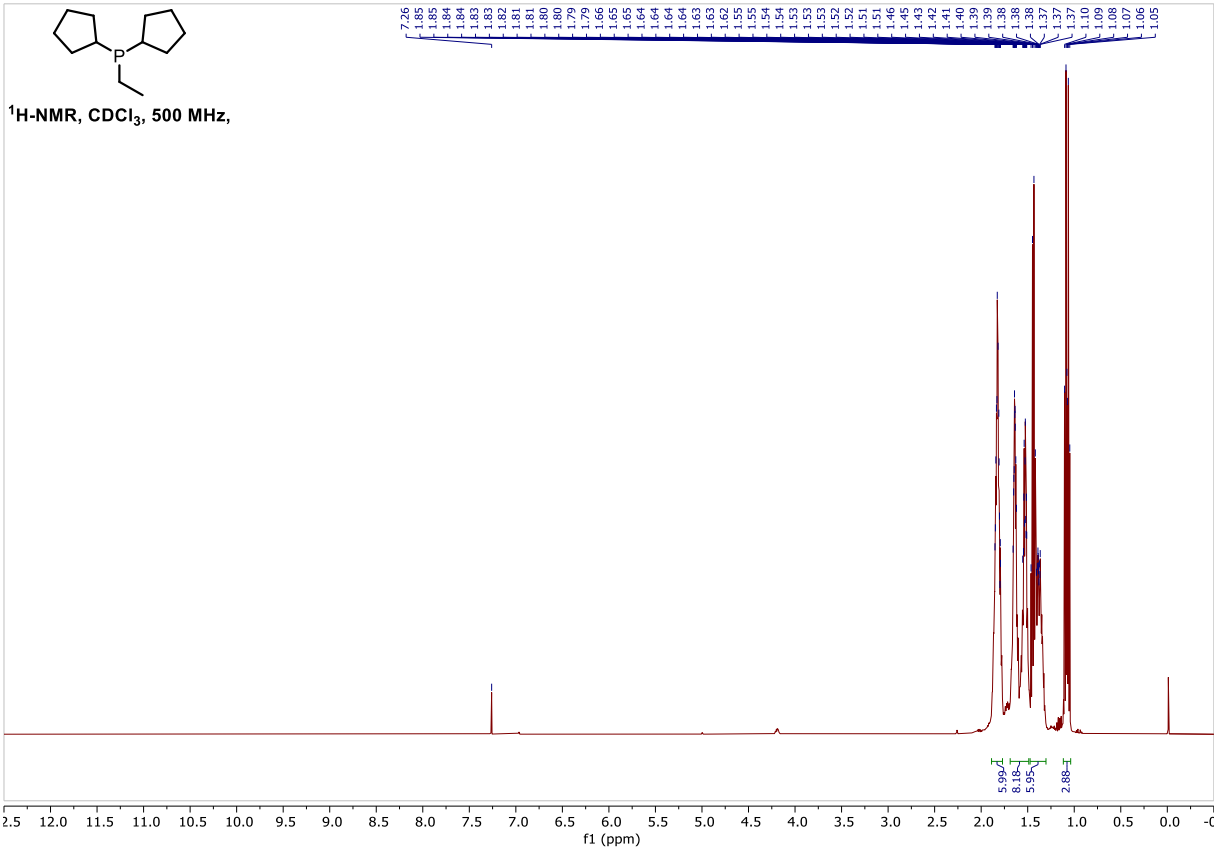
Dicyclopentyl(methyl)phosphine (**L2.45**)

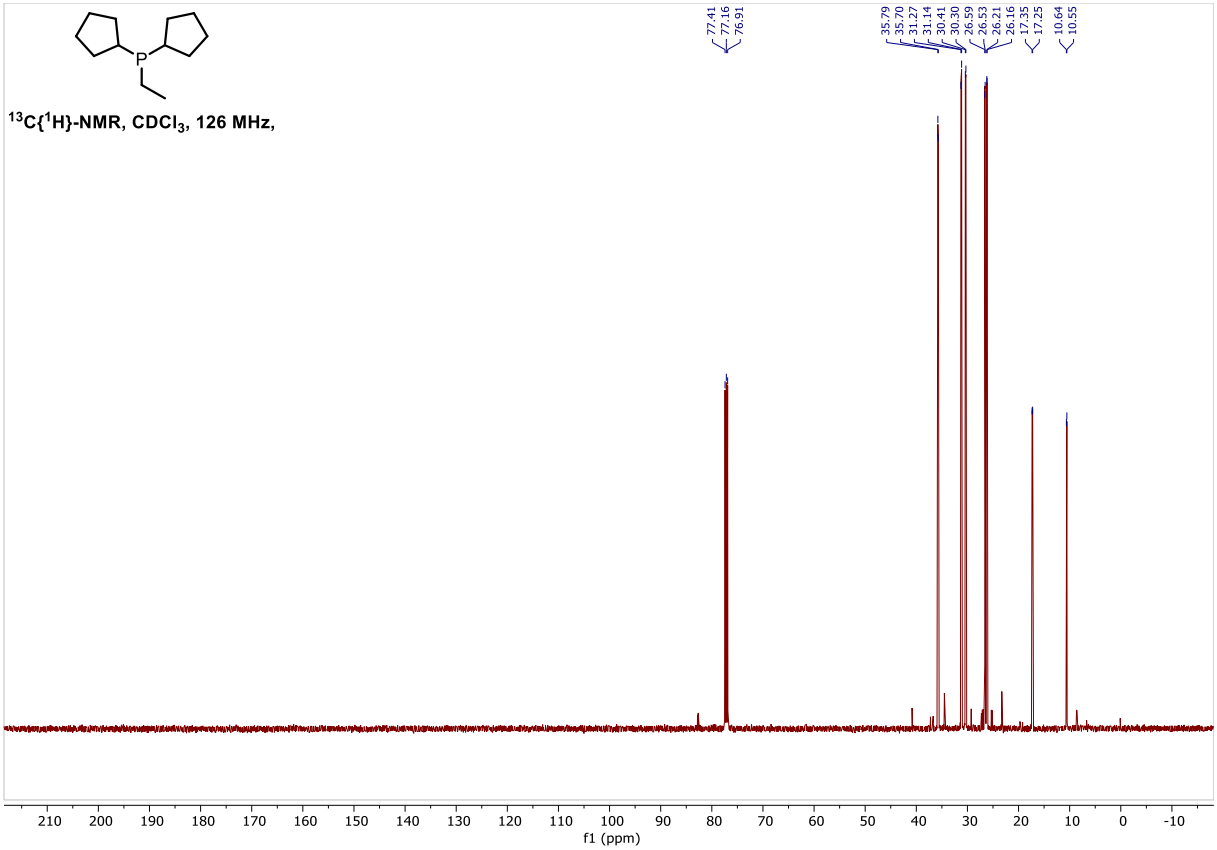




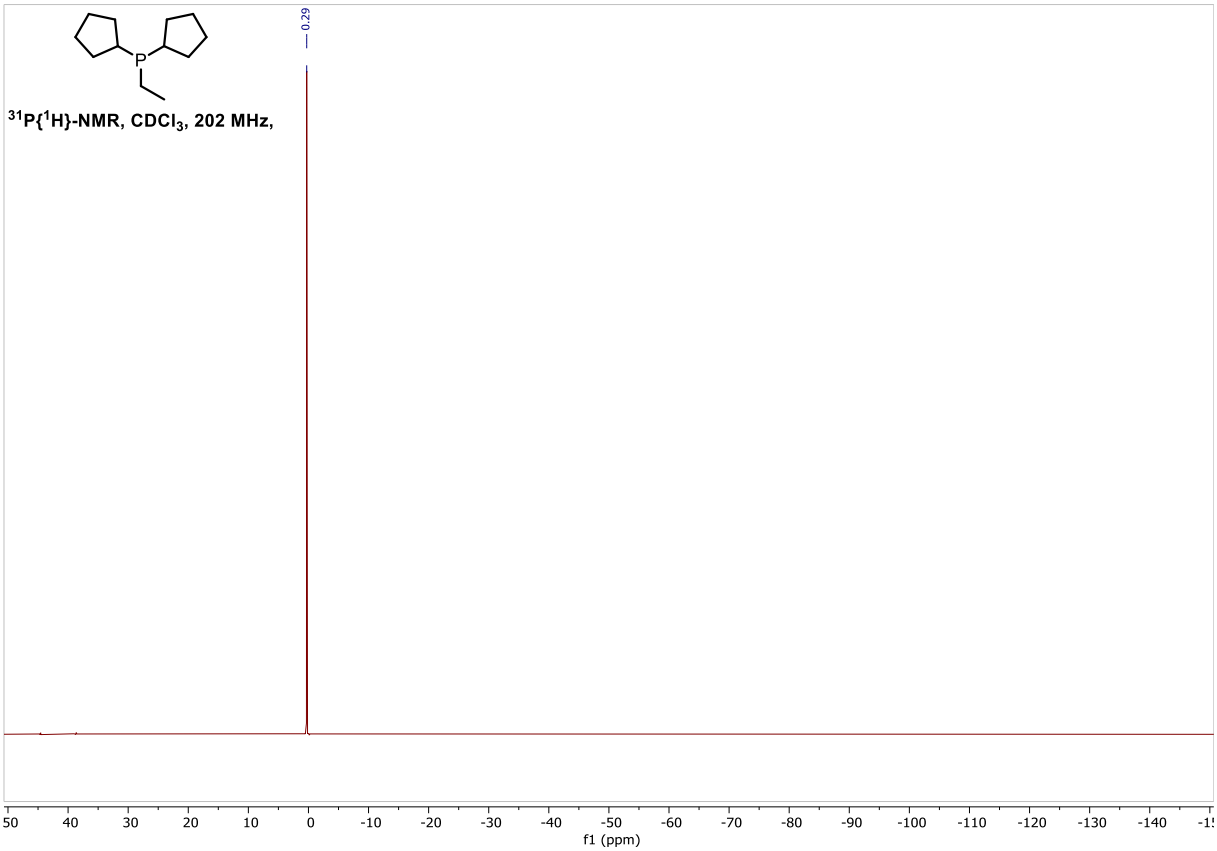


Dicyclopentyl(ethyl)phosphine (**L2.46**)



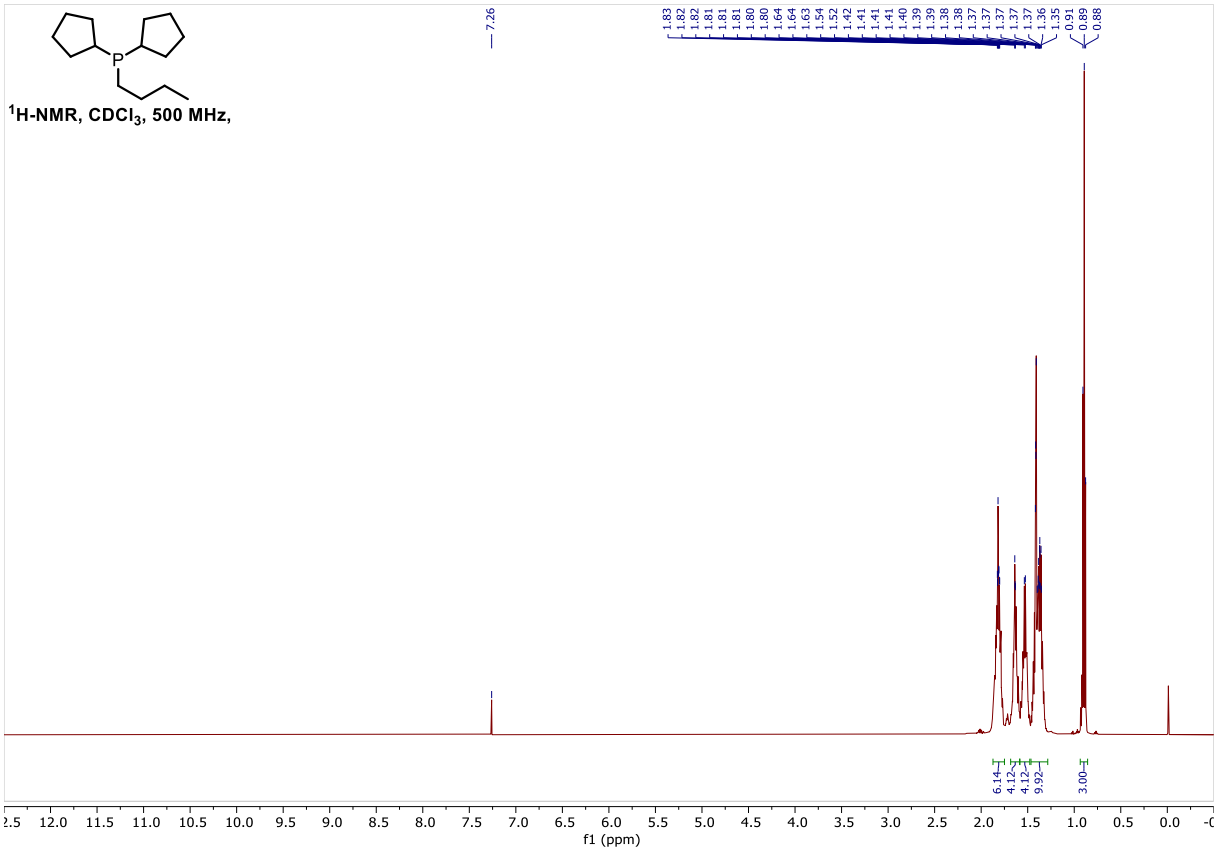


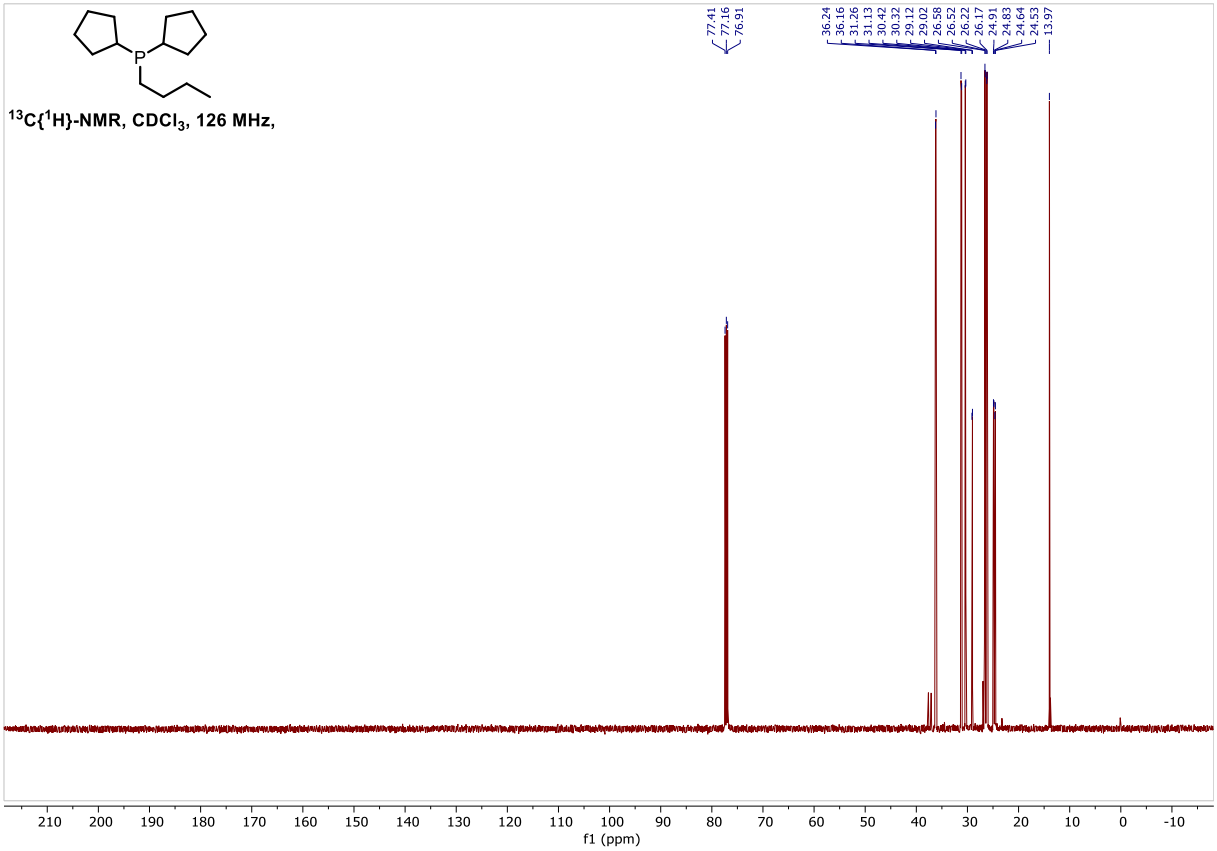
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

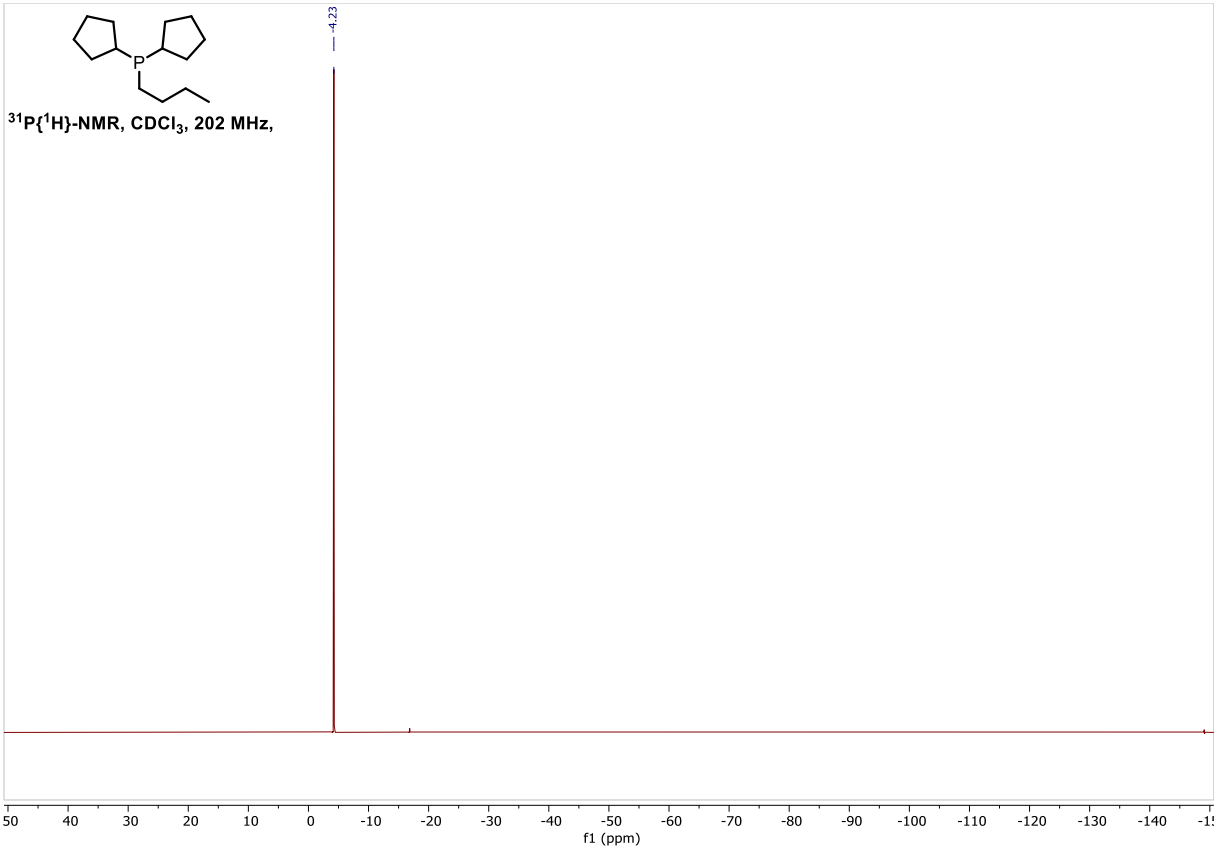


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 202 MHz,

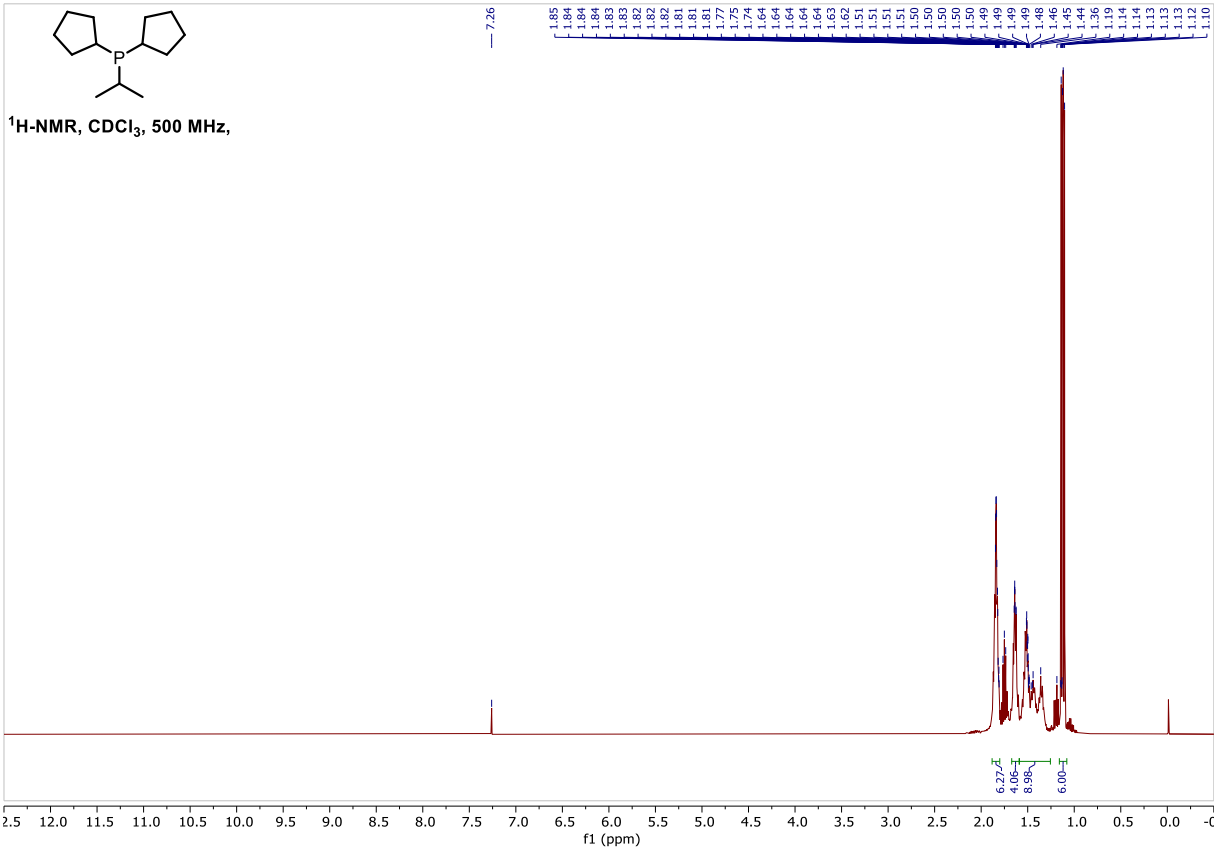
Butyldicyclopentylphosphine (**L2.47**)

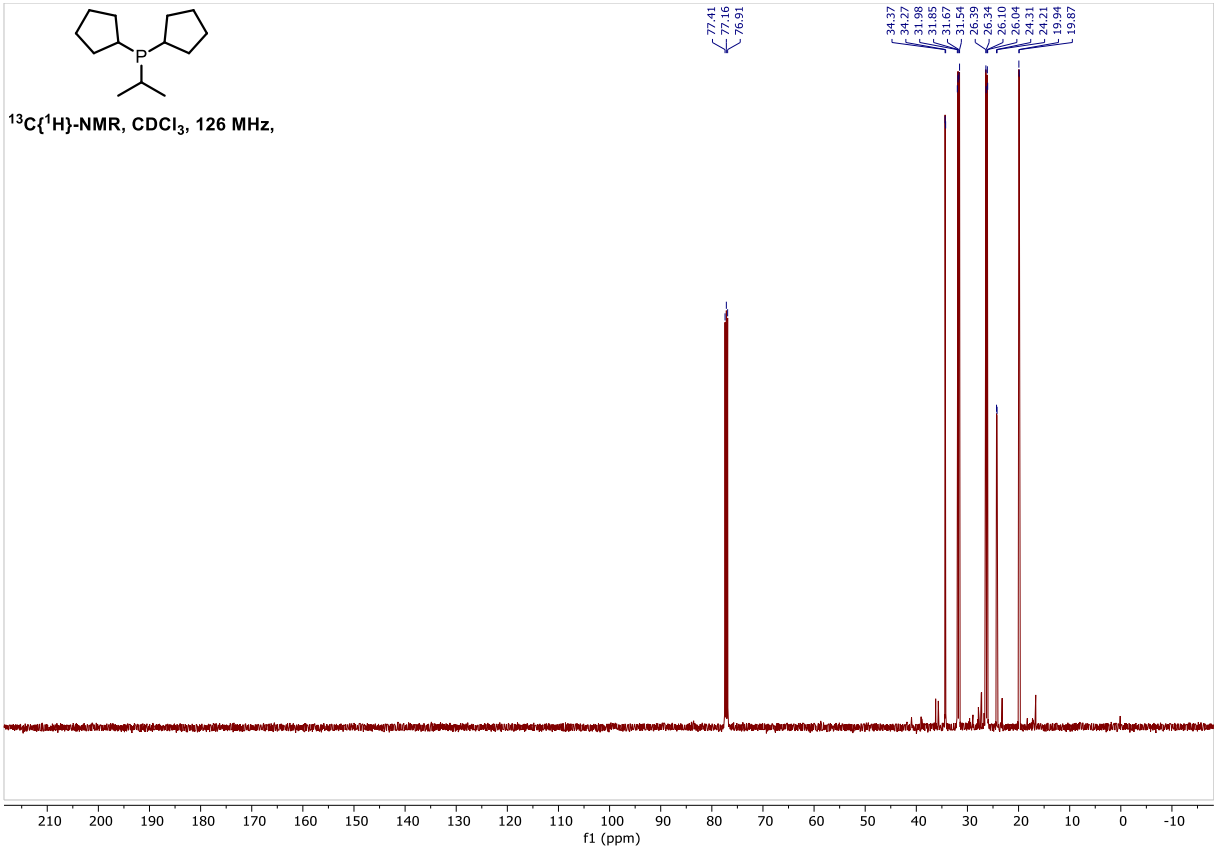




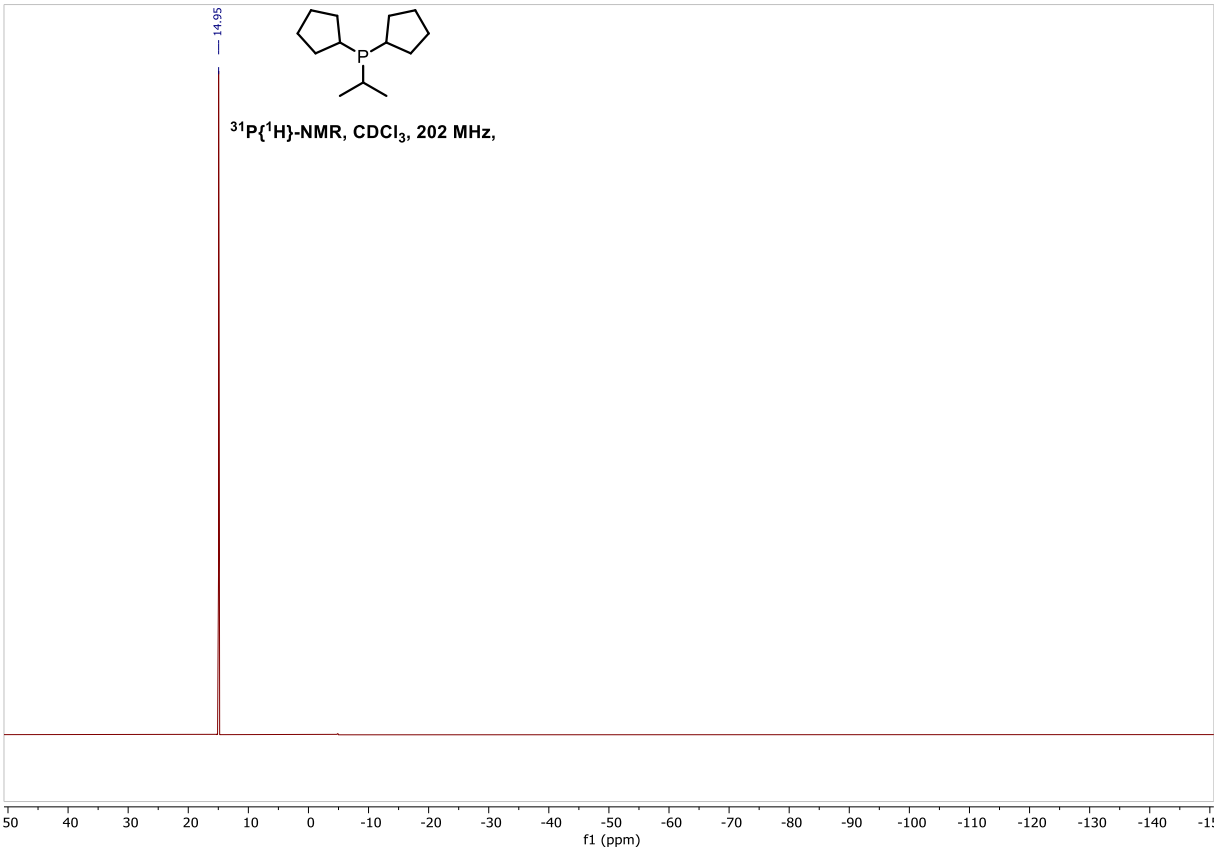


Dicyclopentyl(isopropyl)phosphine (**L2.48**)



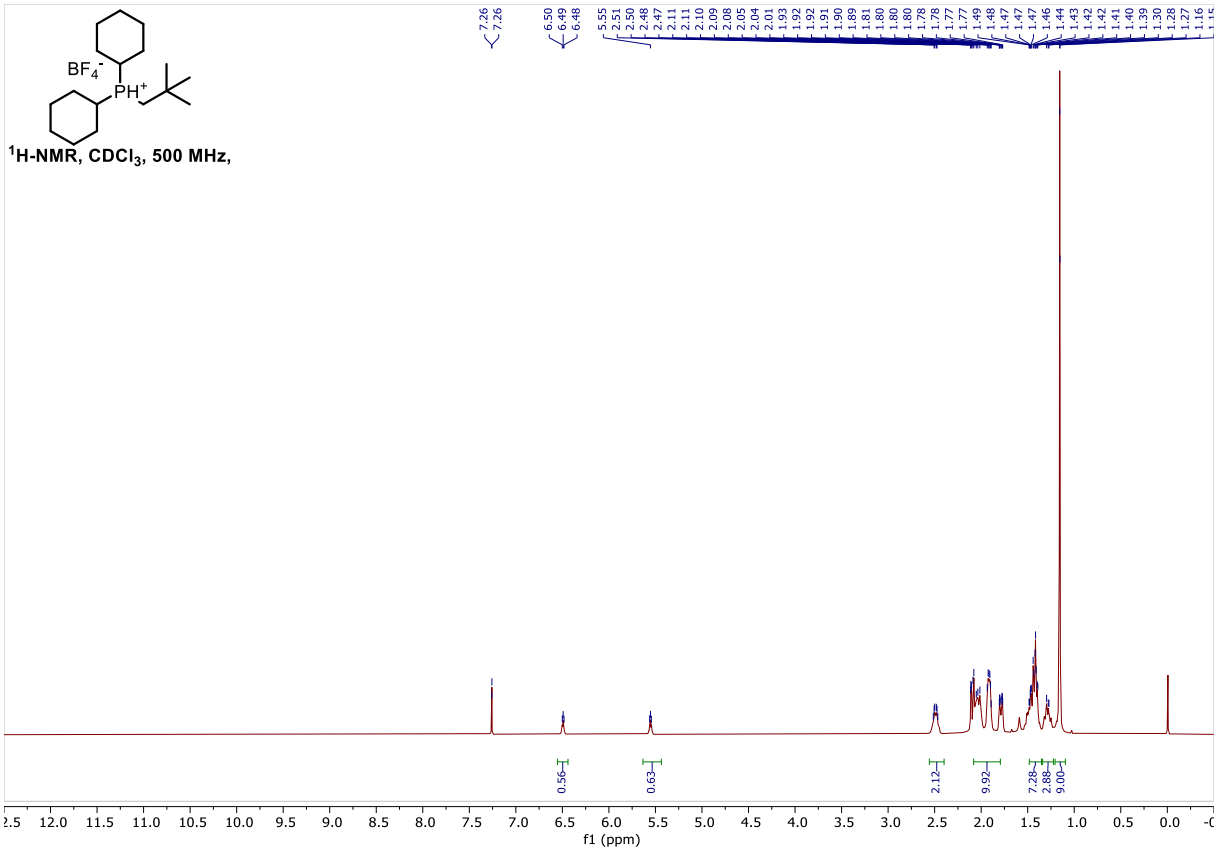


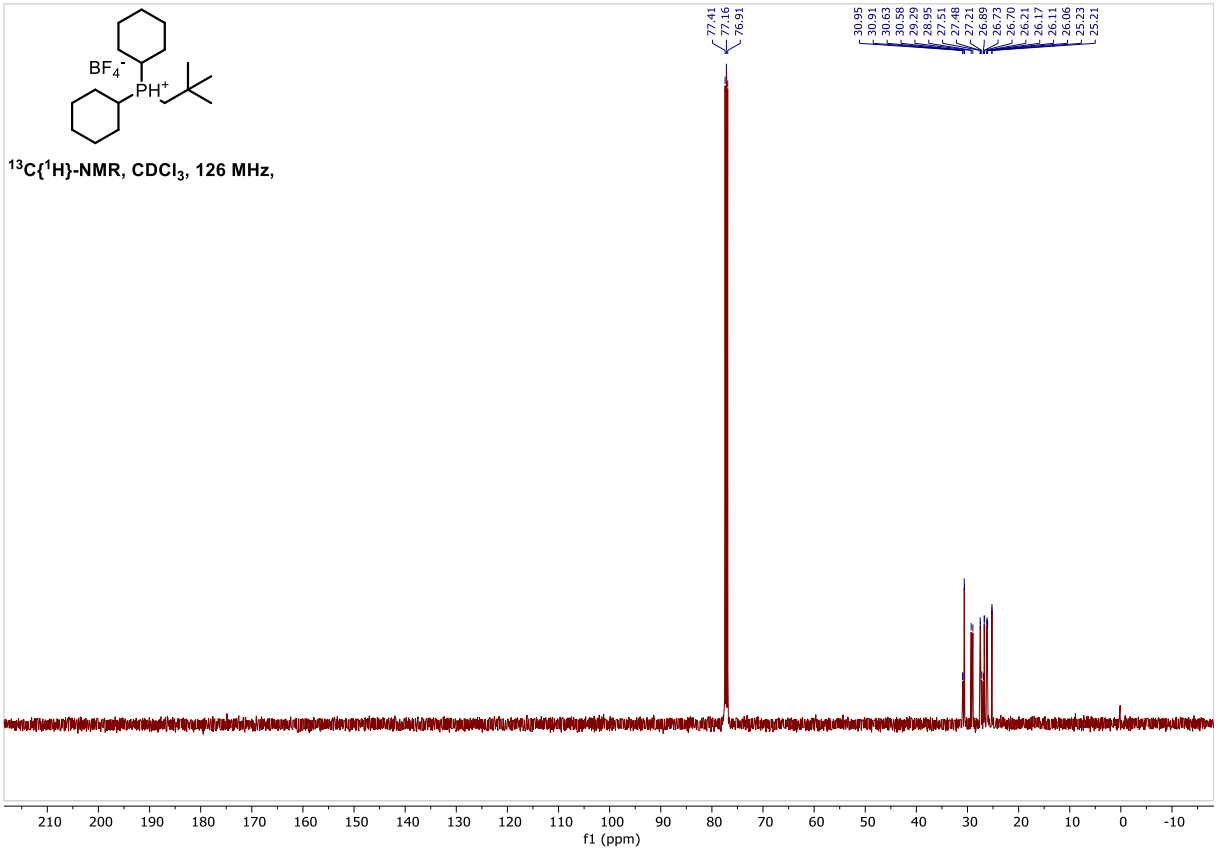
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

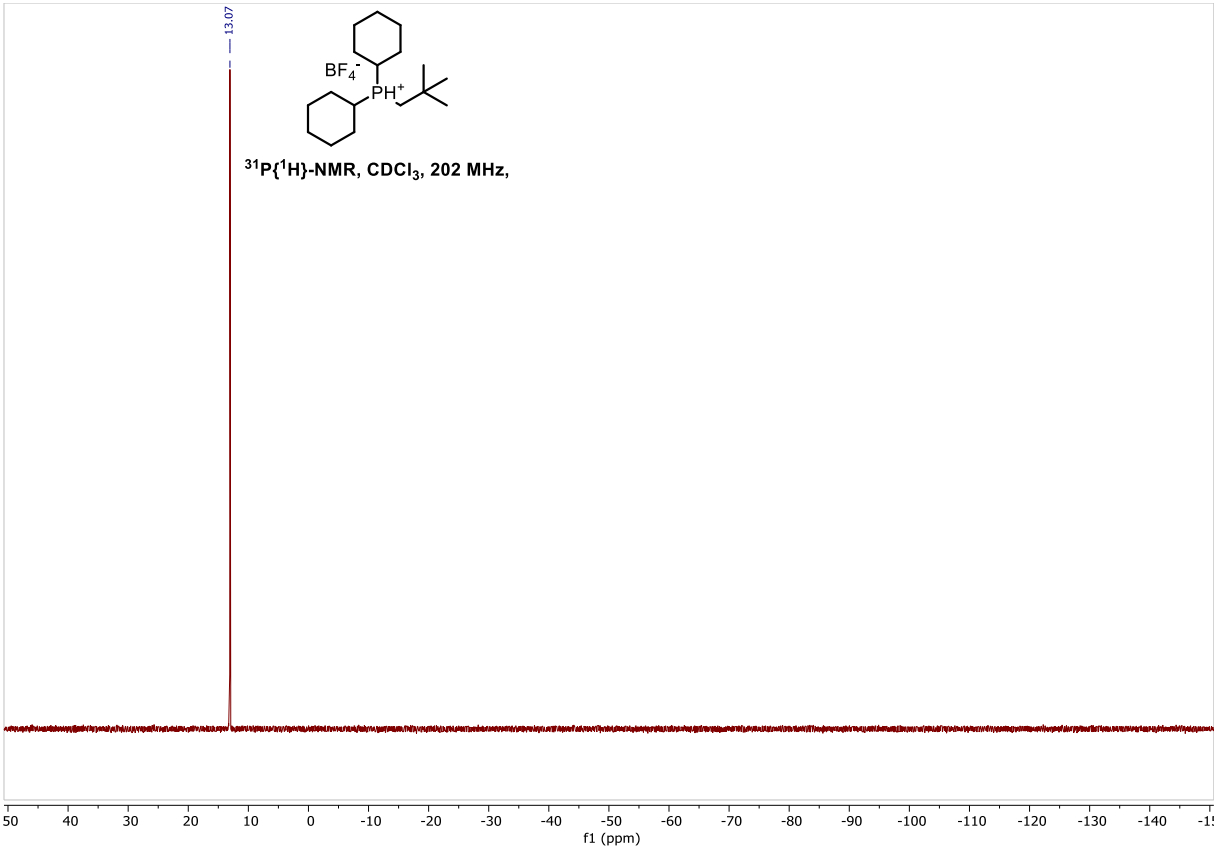


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 202 MHz,

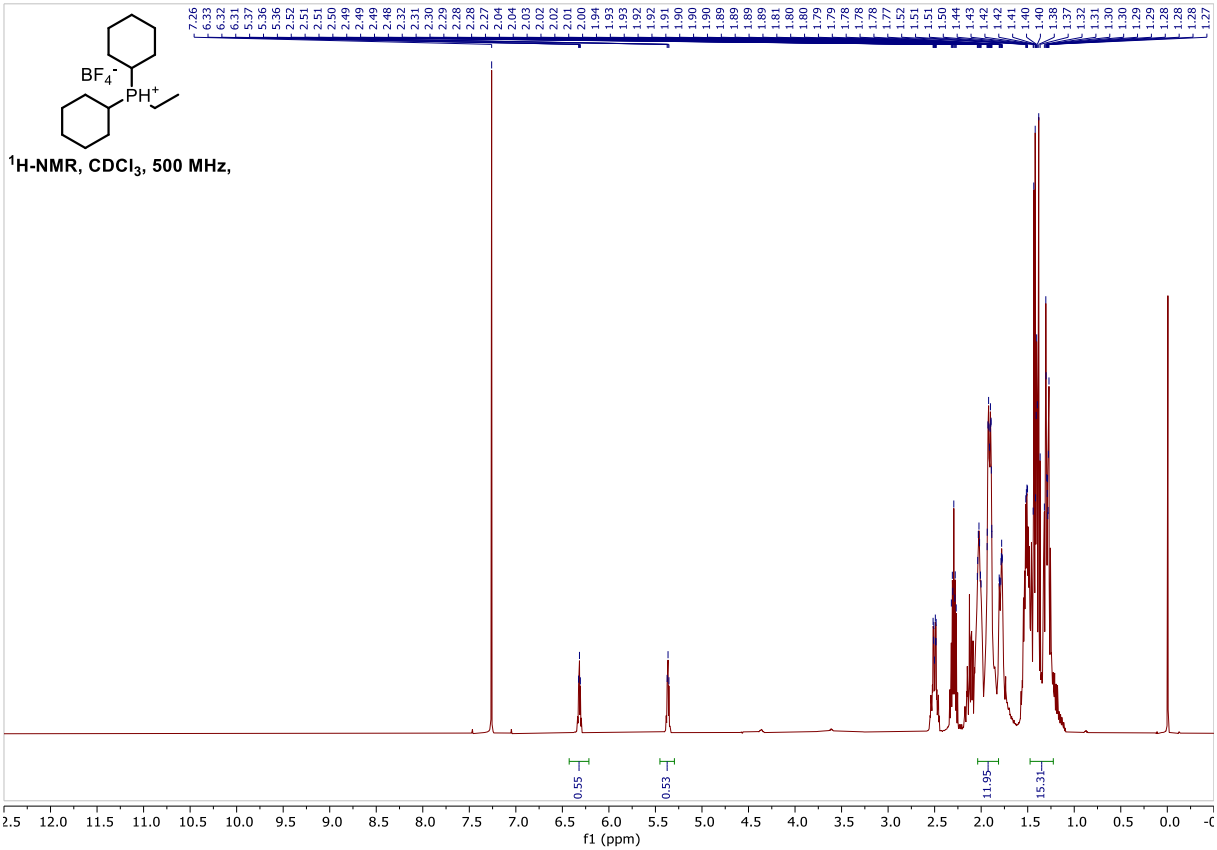
Dicyclohexyl(neopentyl)phosphine tetrafluoroborate (**L2.49**)

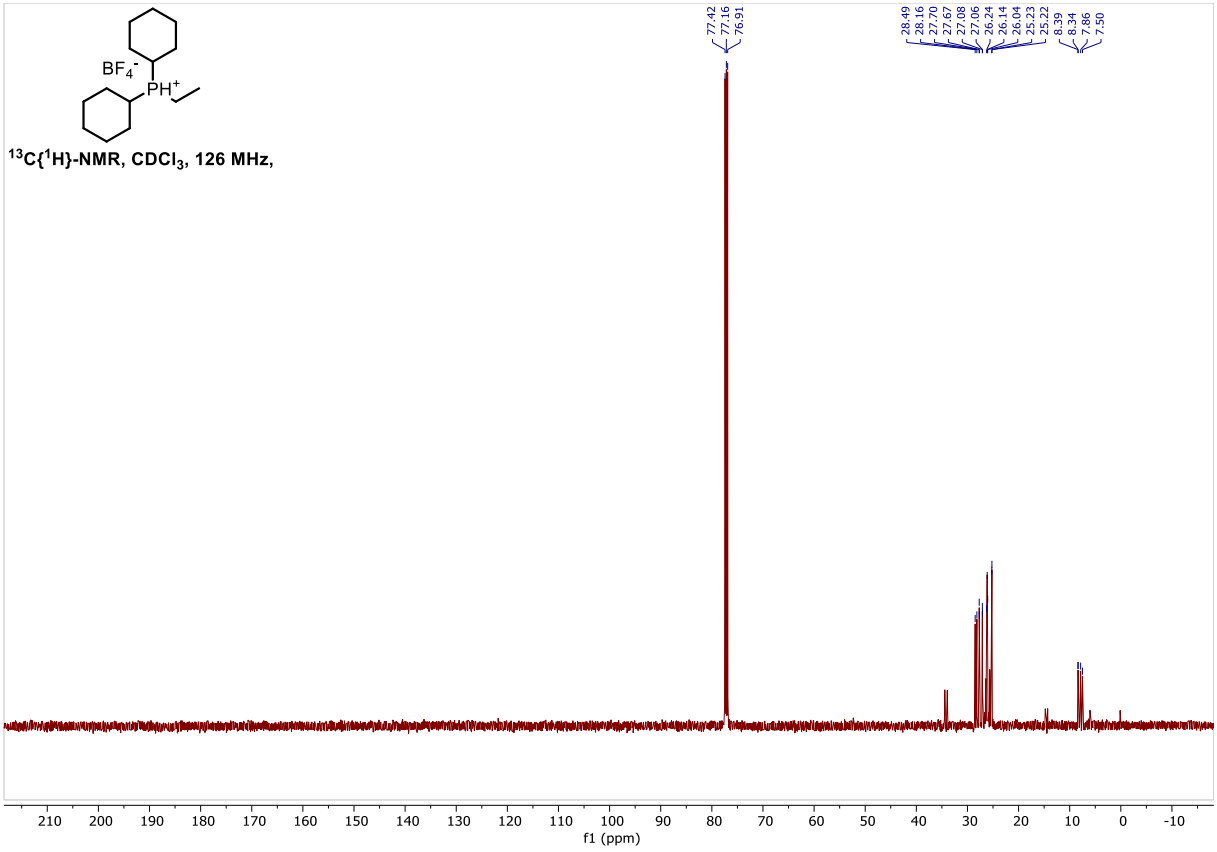




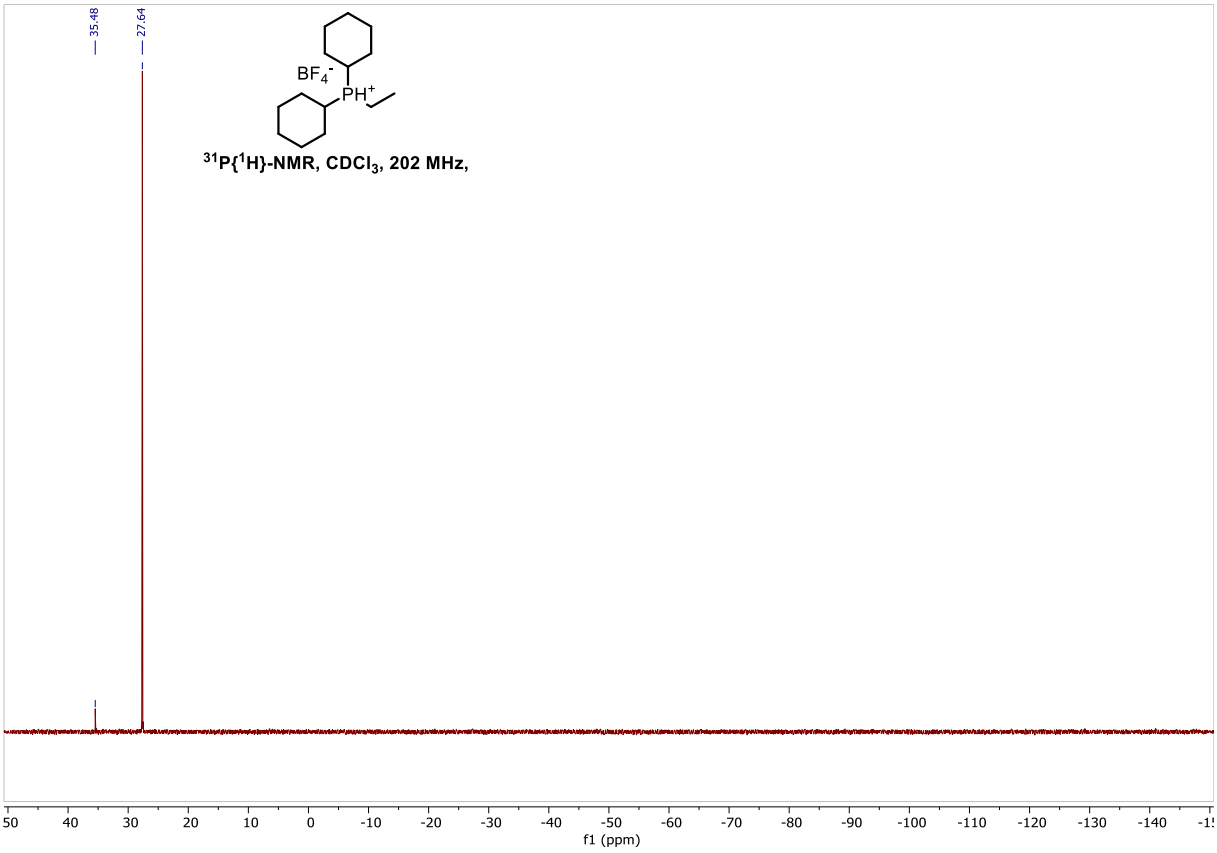


Dicyclohexyl(ethyl)phosphine tetrafluoroborate (**L2.50**)



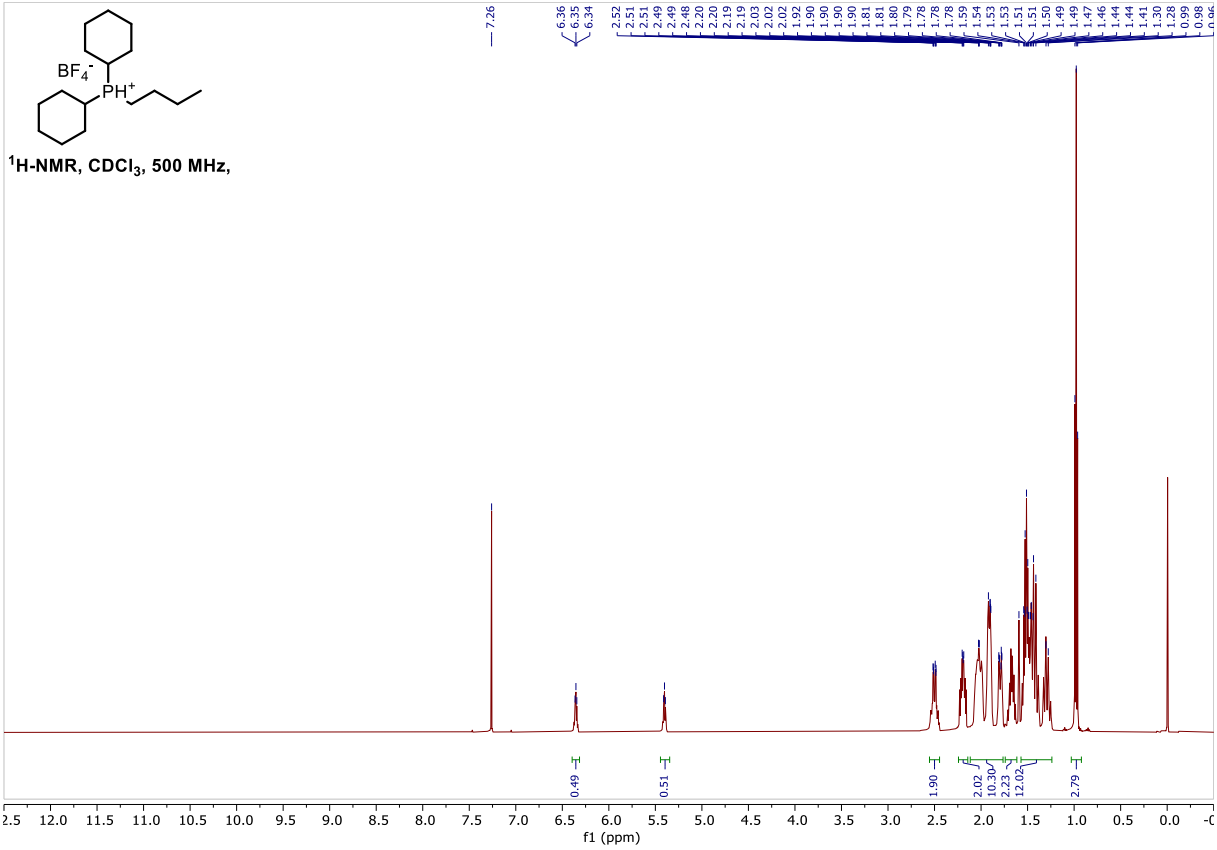


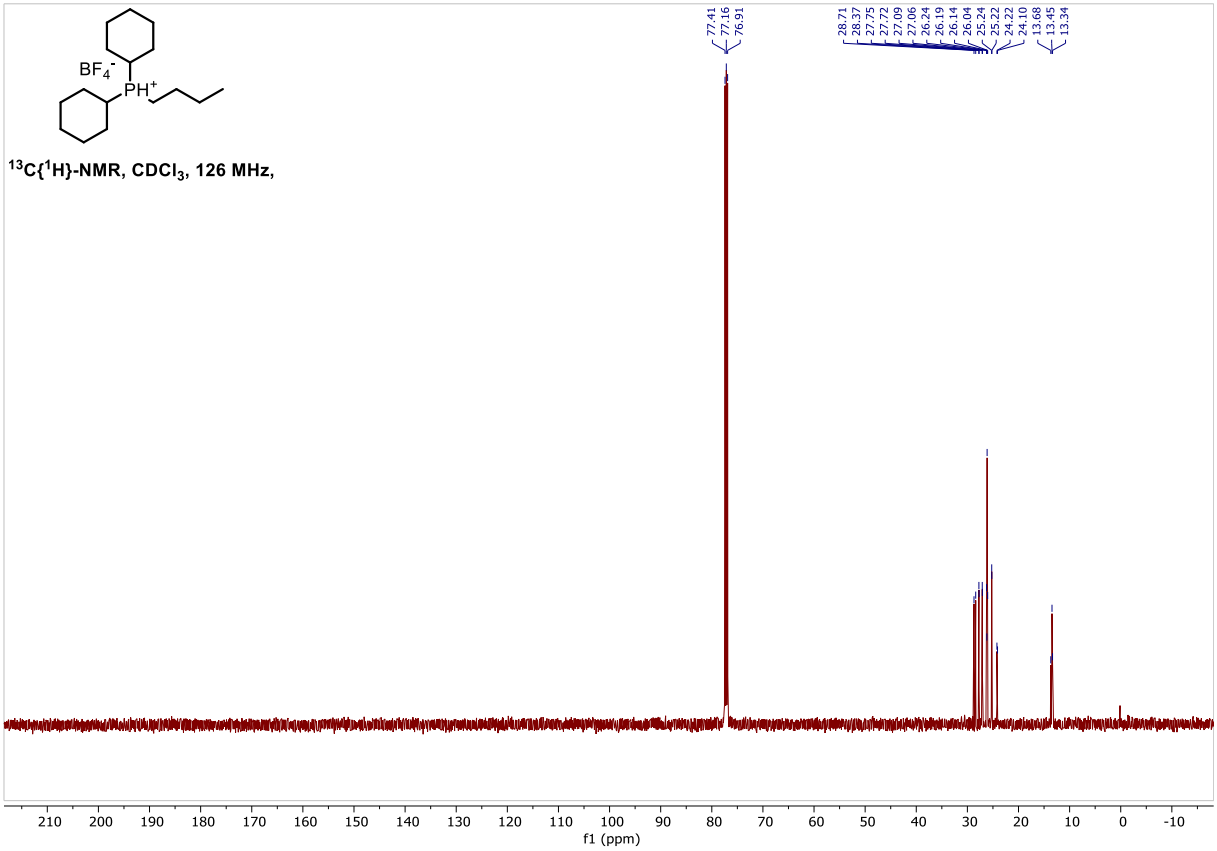
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

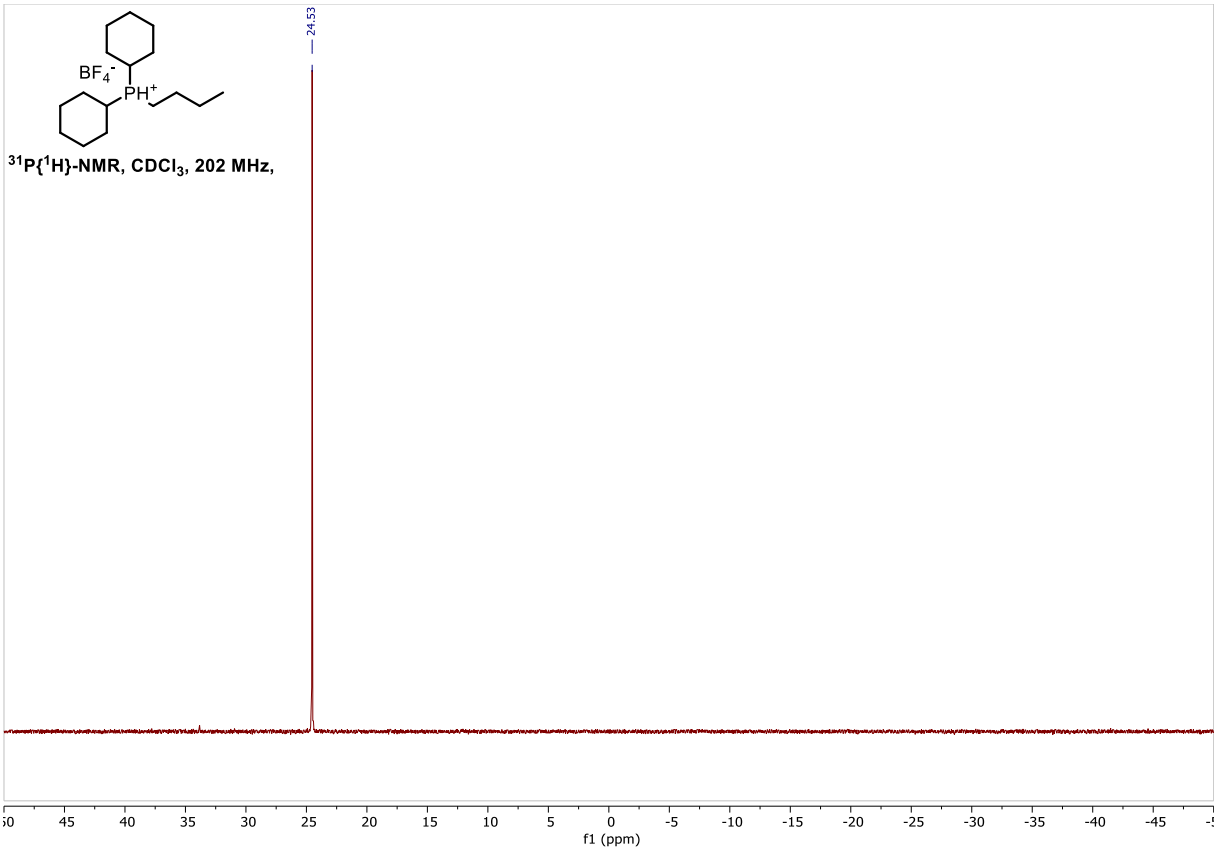


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 202 MHz,

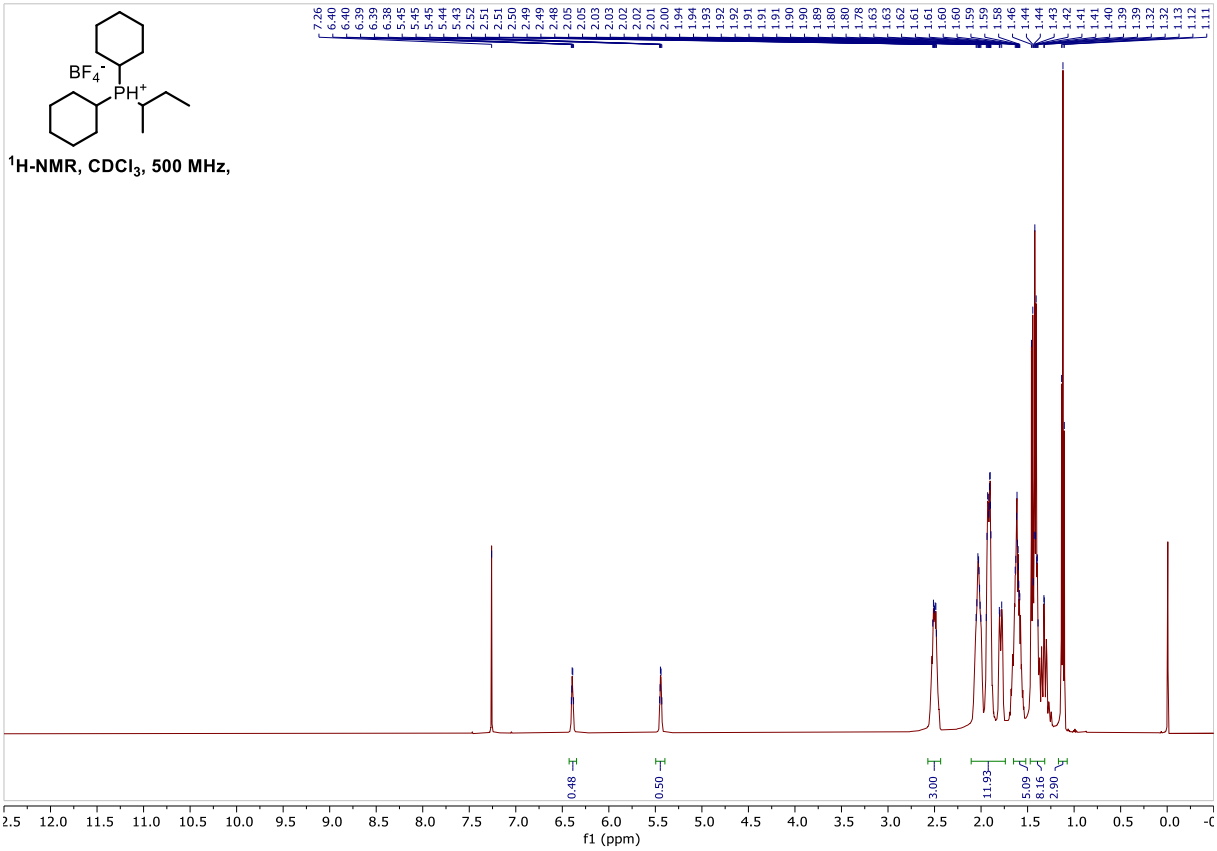
Butyldicyclohexylphosphine tetrafluoroborate (**L2.51**)

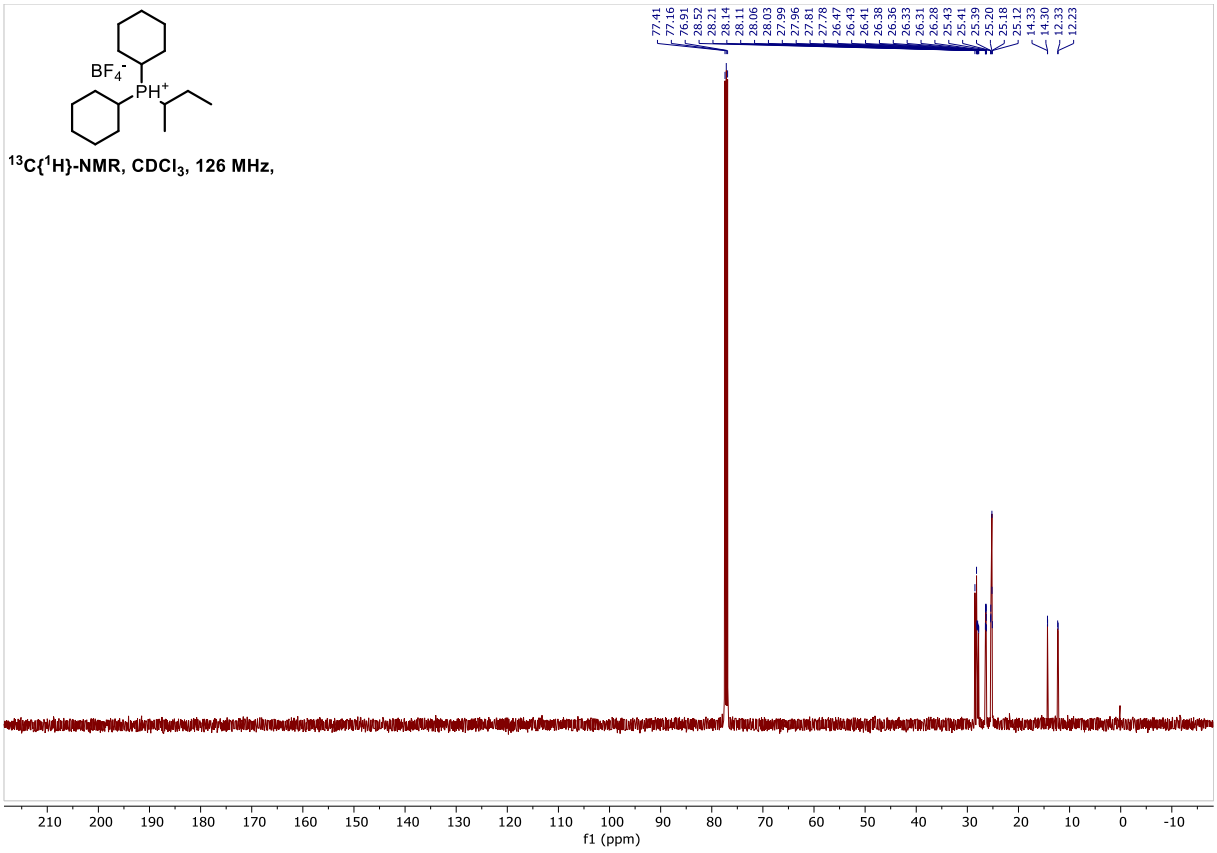




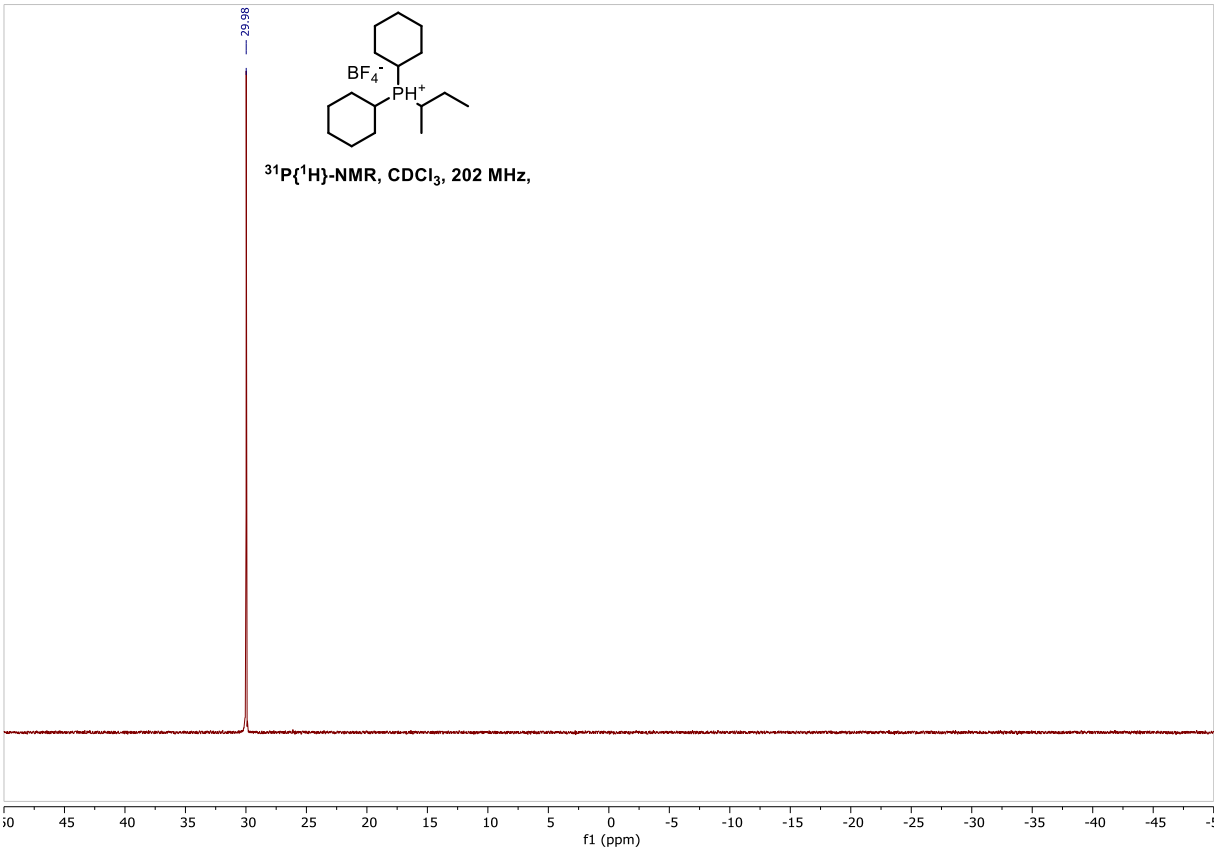


sec-Butyldicyclohexylphosphine tetrafluoroborate (**L2.52**)



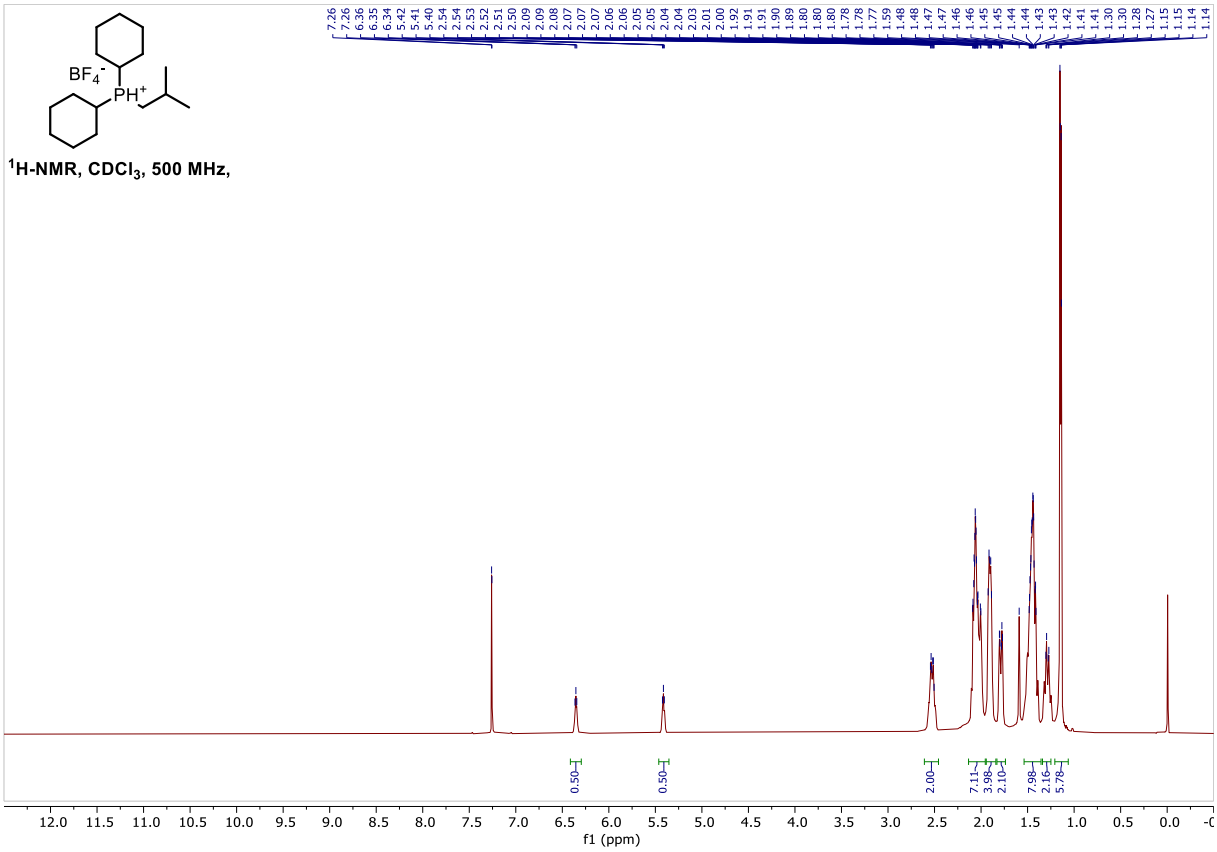


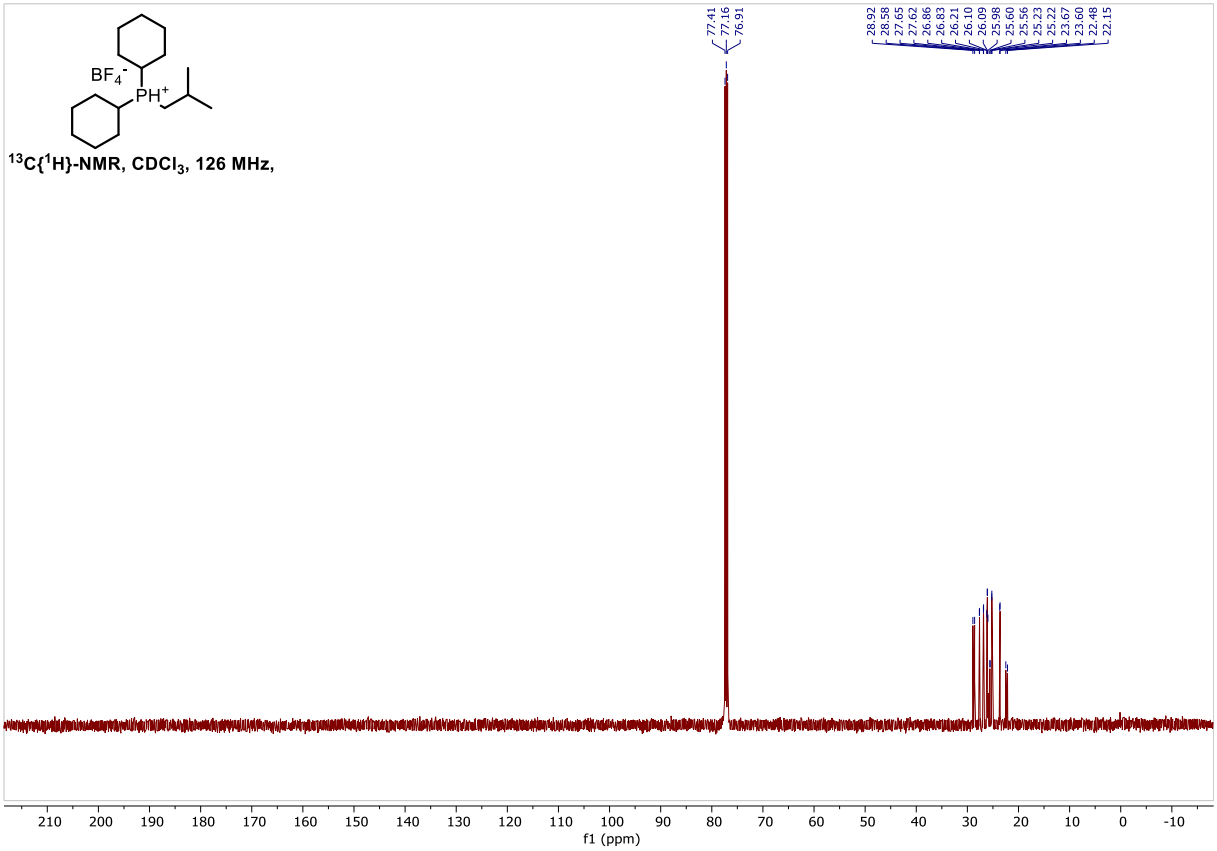
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

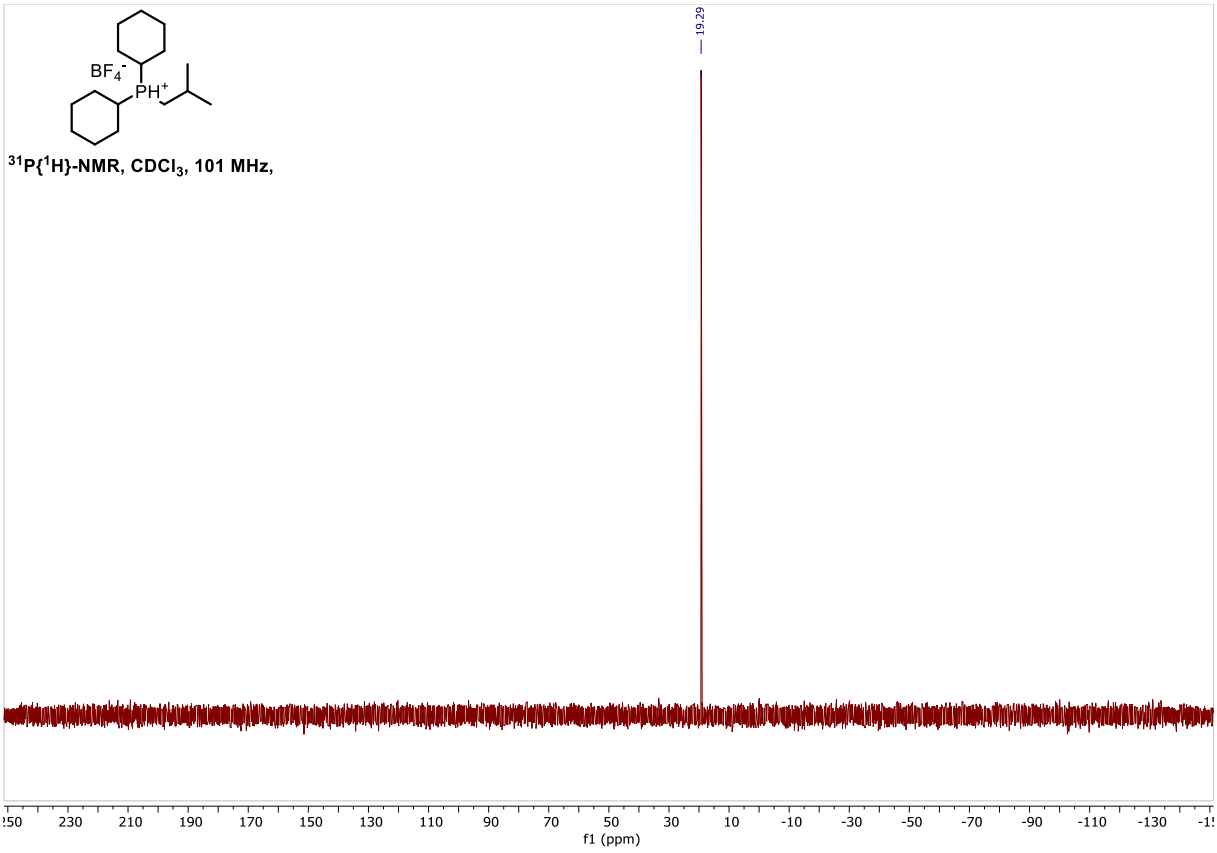


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 202 MHz,

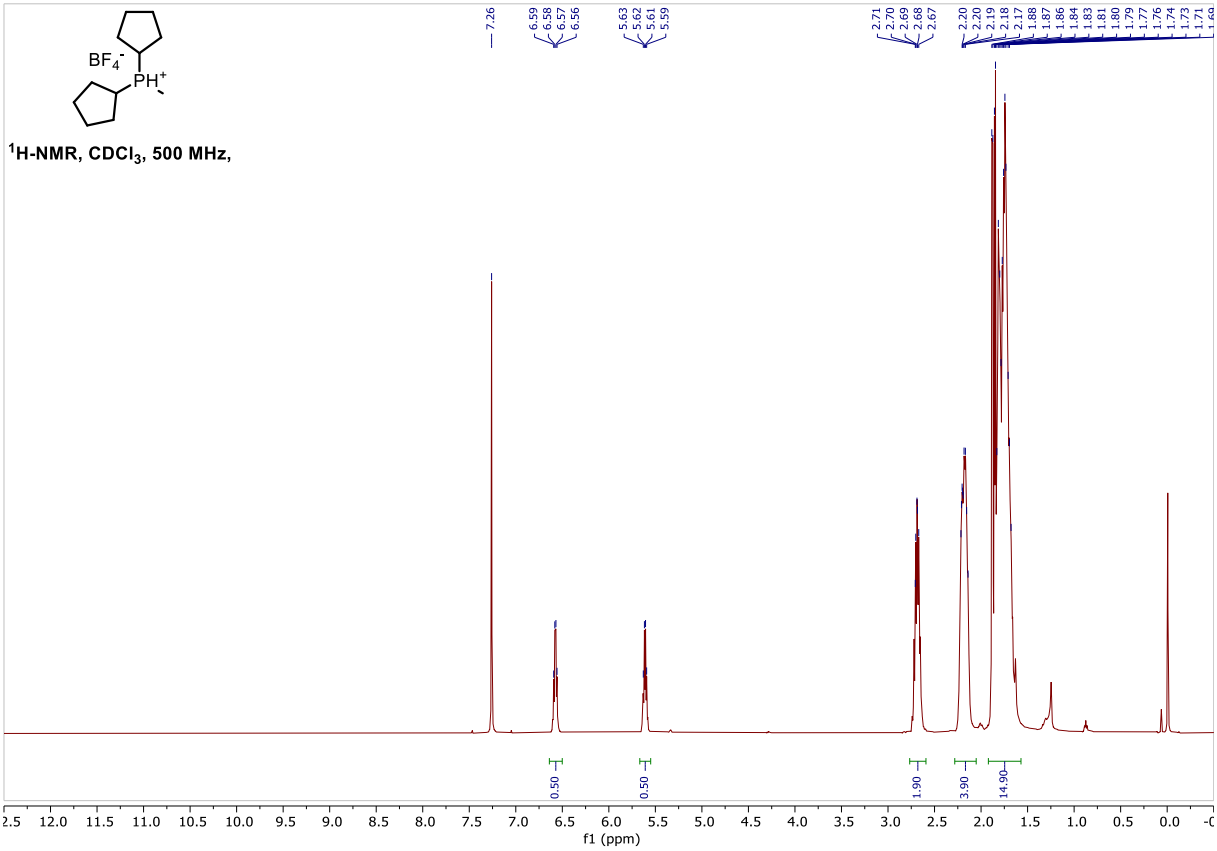
Dicyclohexyl(*iso*butyl)phosphine tetrafluoroborate (**L2.53**)

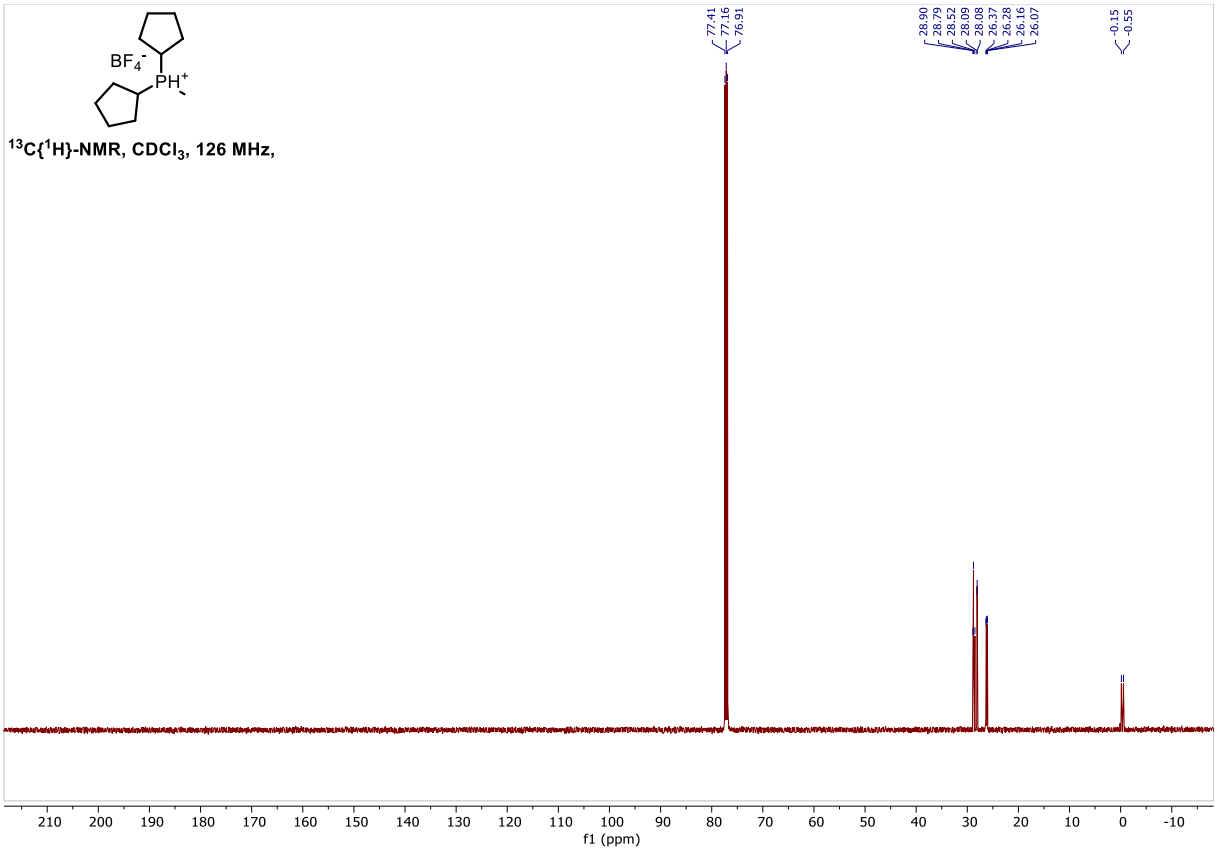




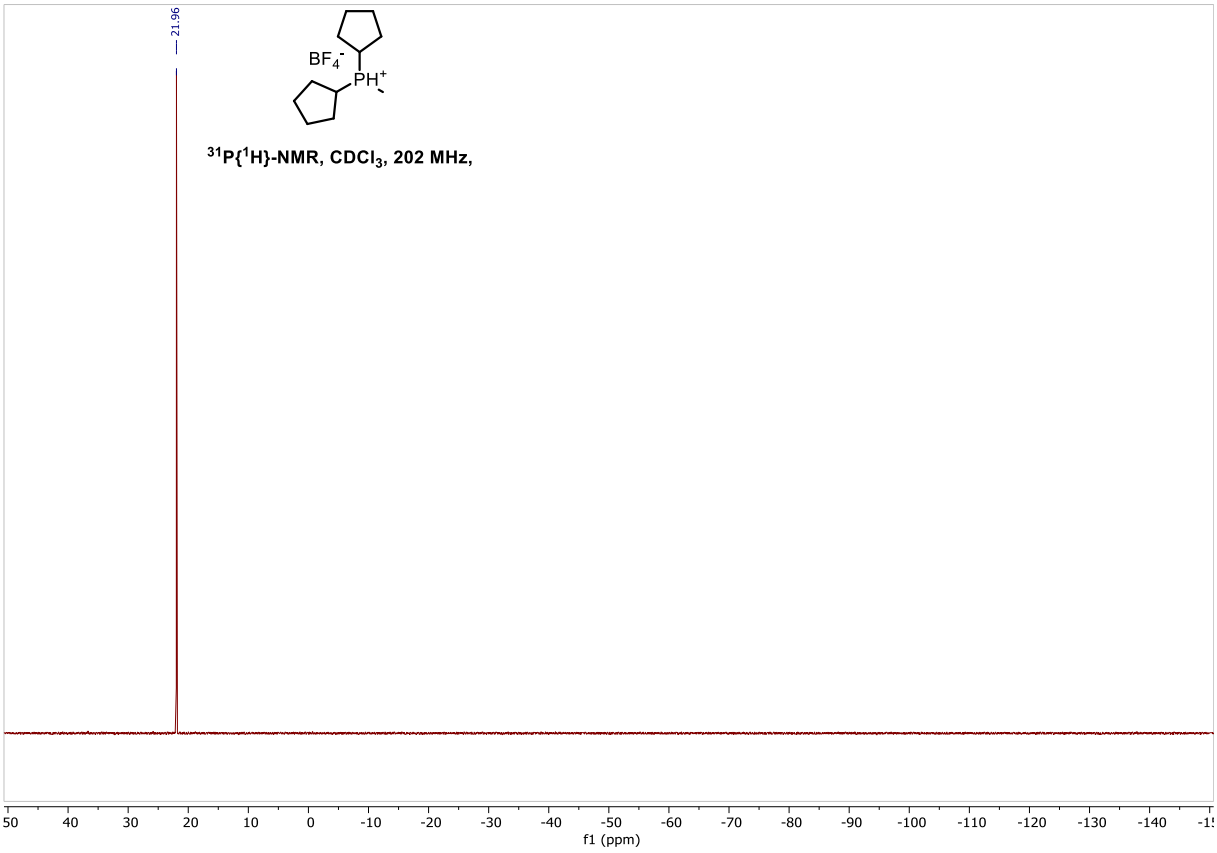


Dicyclopentyl(methyl)phosphine tetrafluoroborate (**L2.54**)



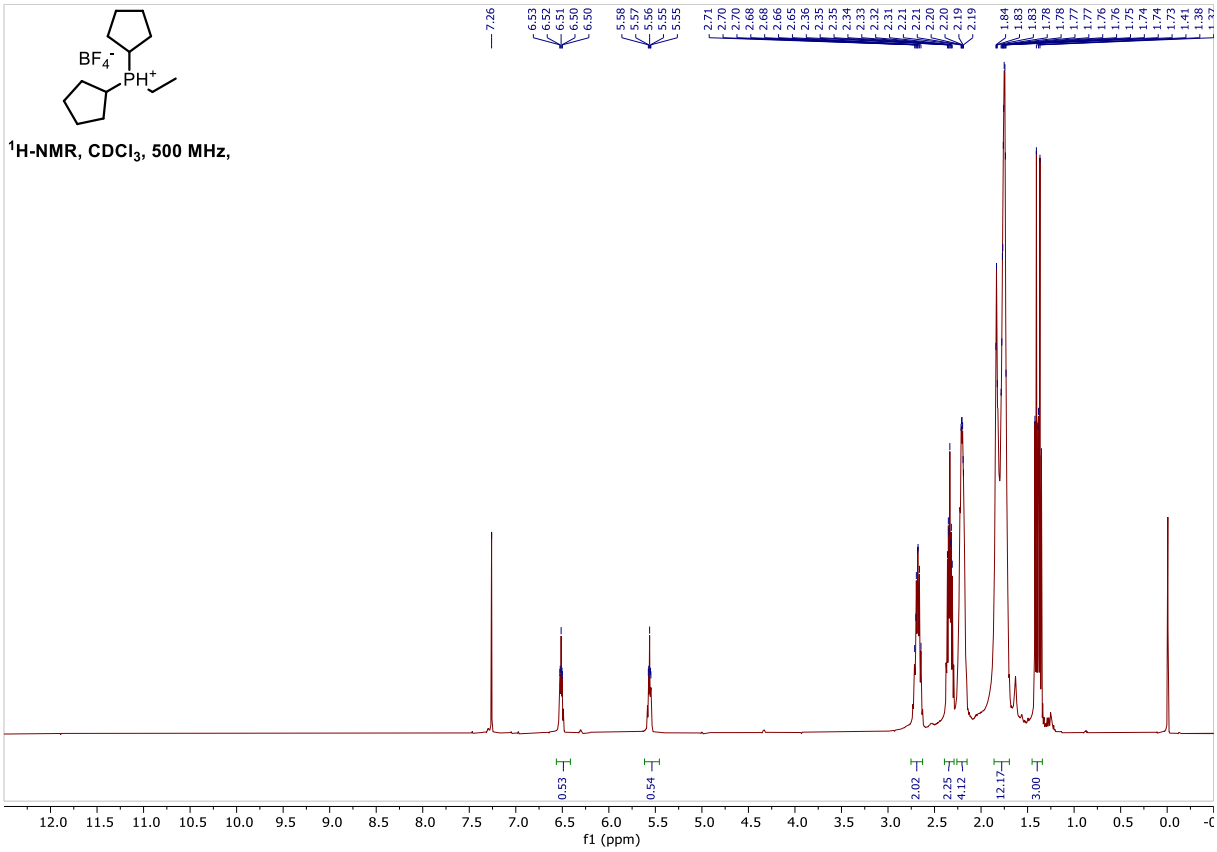


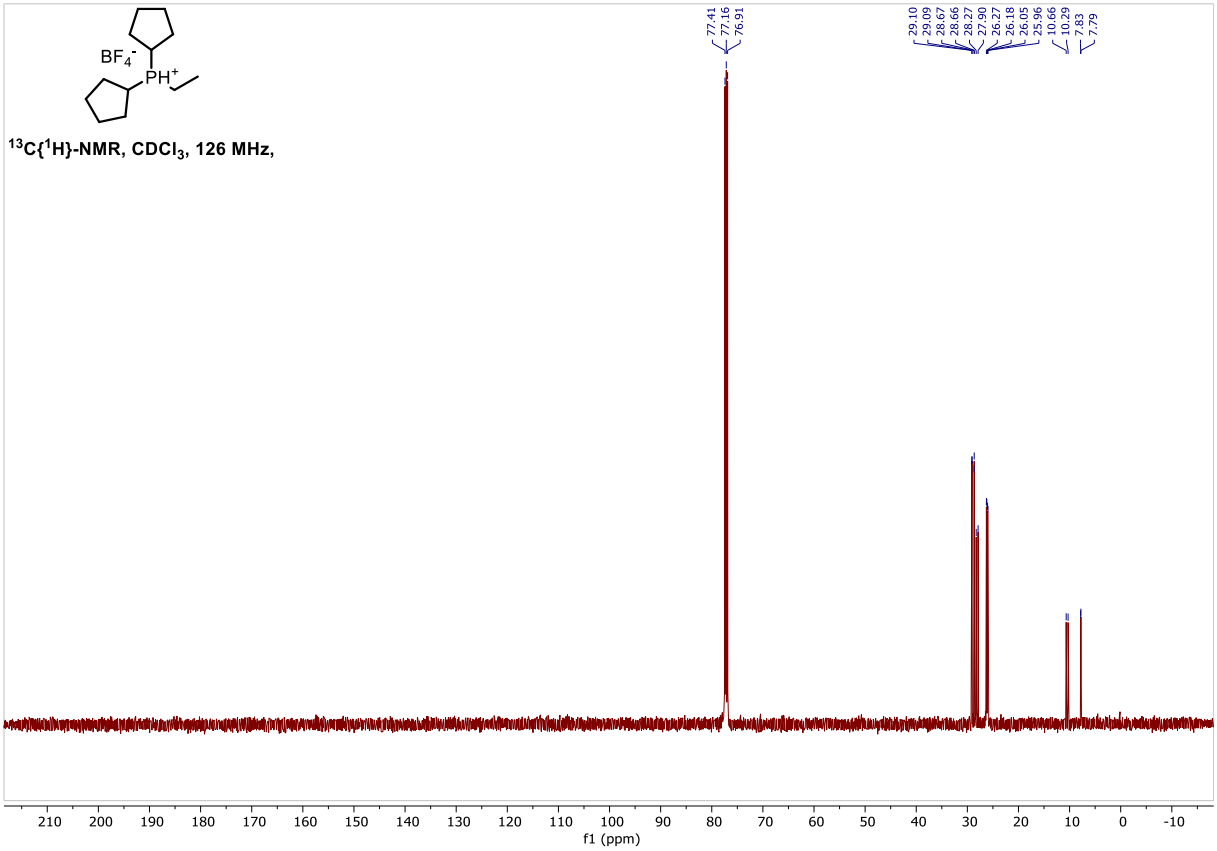
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz,

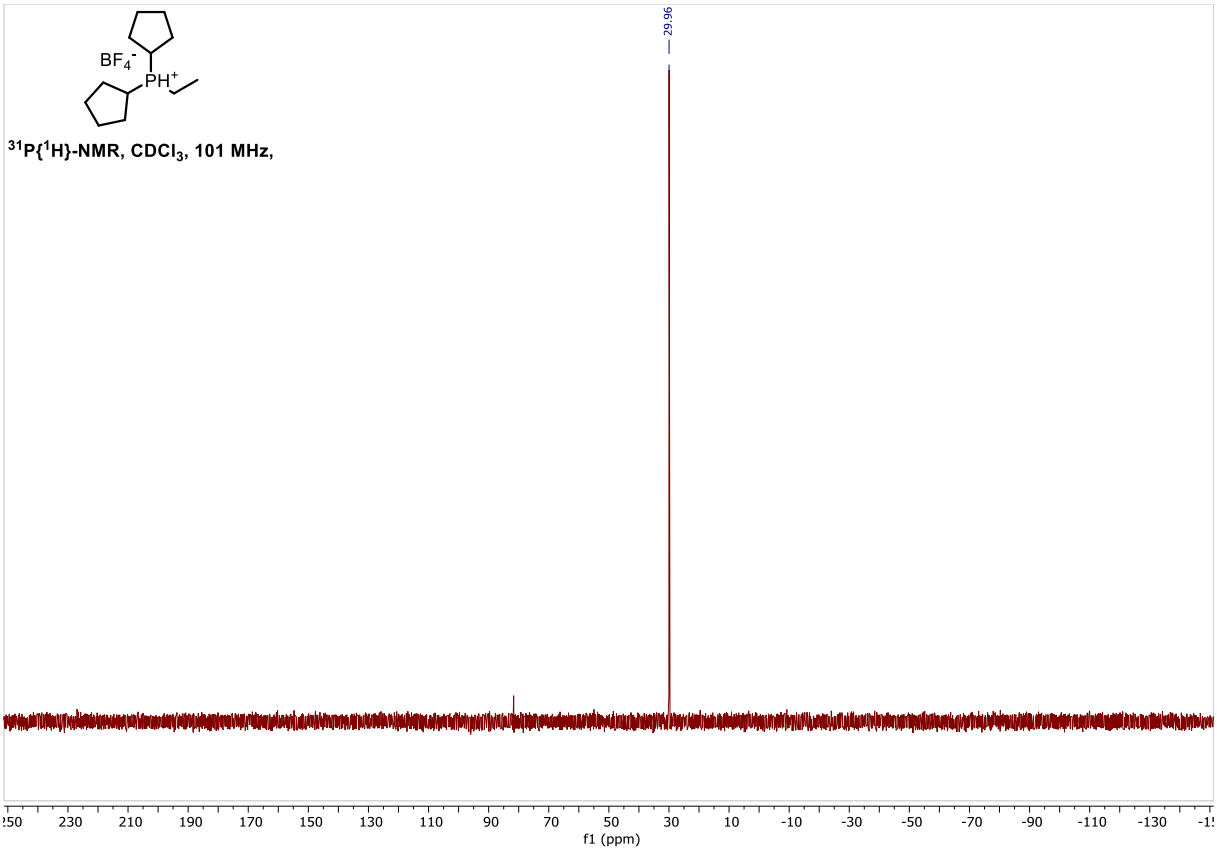


$^{31}P\{^{1}H\}$-NMR, $CDCl_3$, 202 MHz,

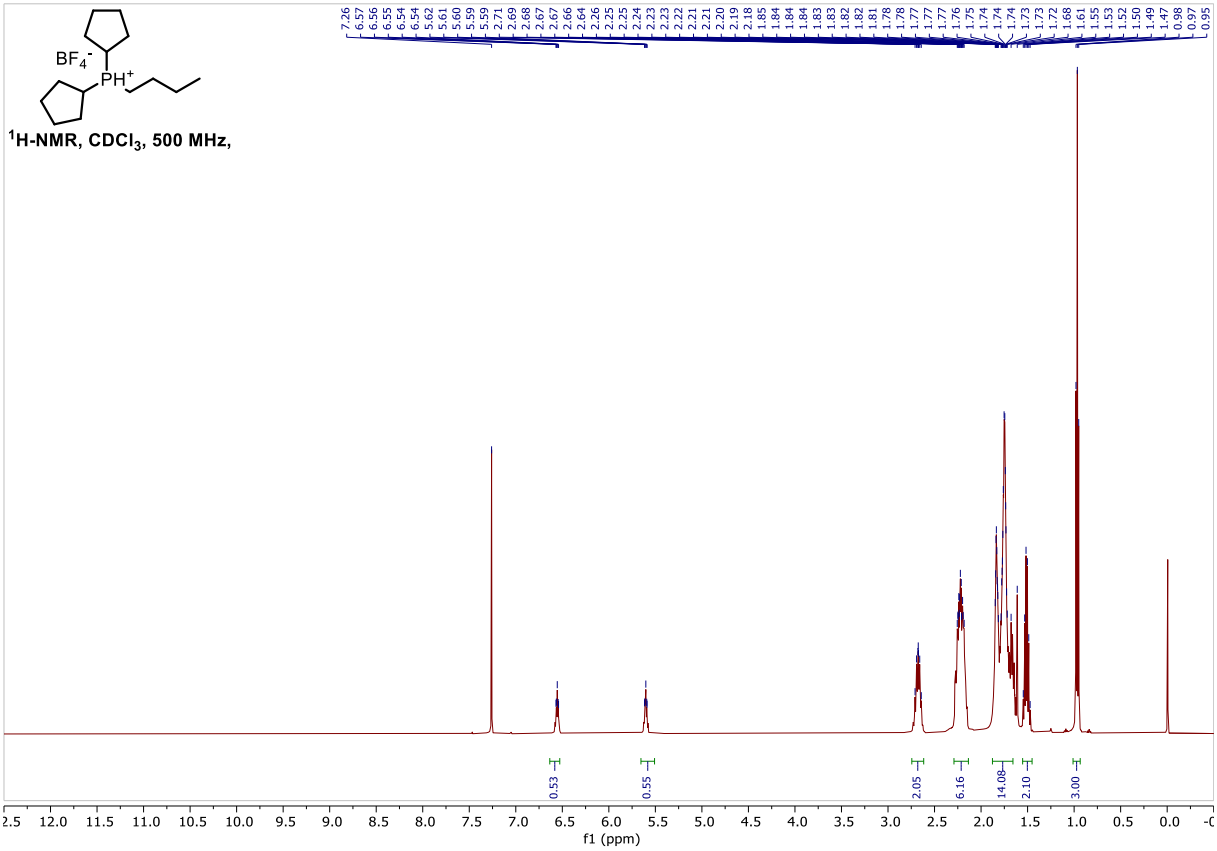
Dicyclopentyl(ethyl)phosphine tetrafluoroborate (**L2.55**)

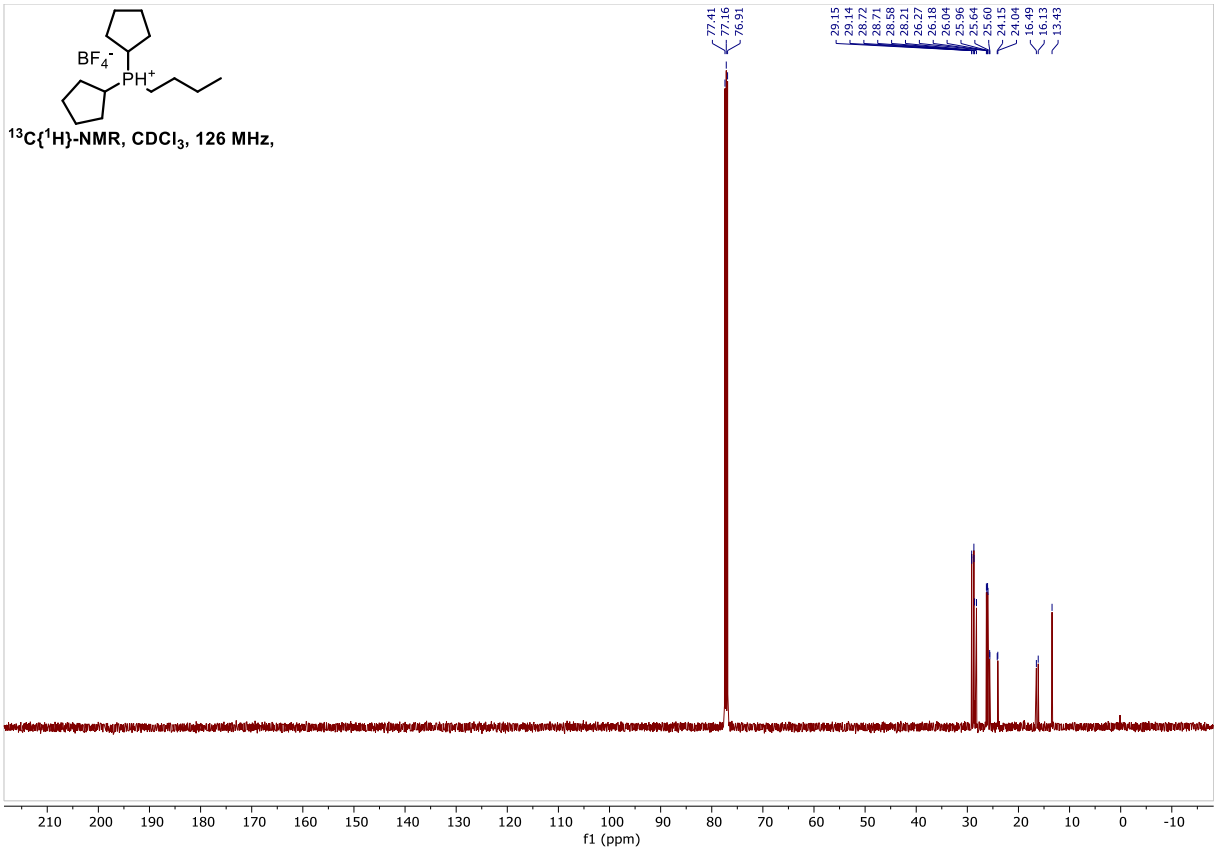


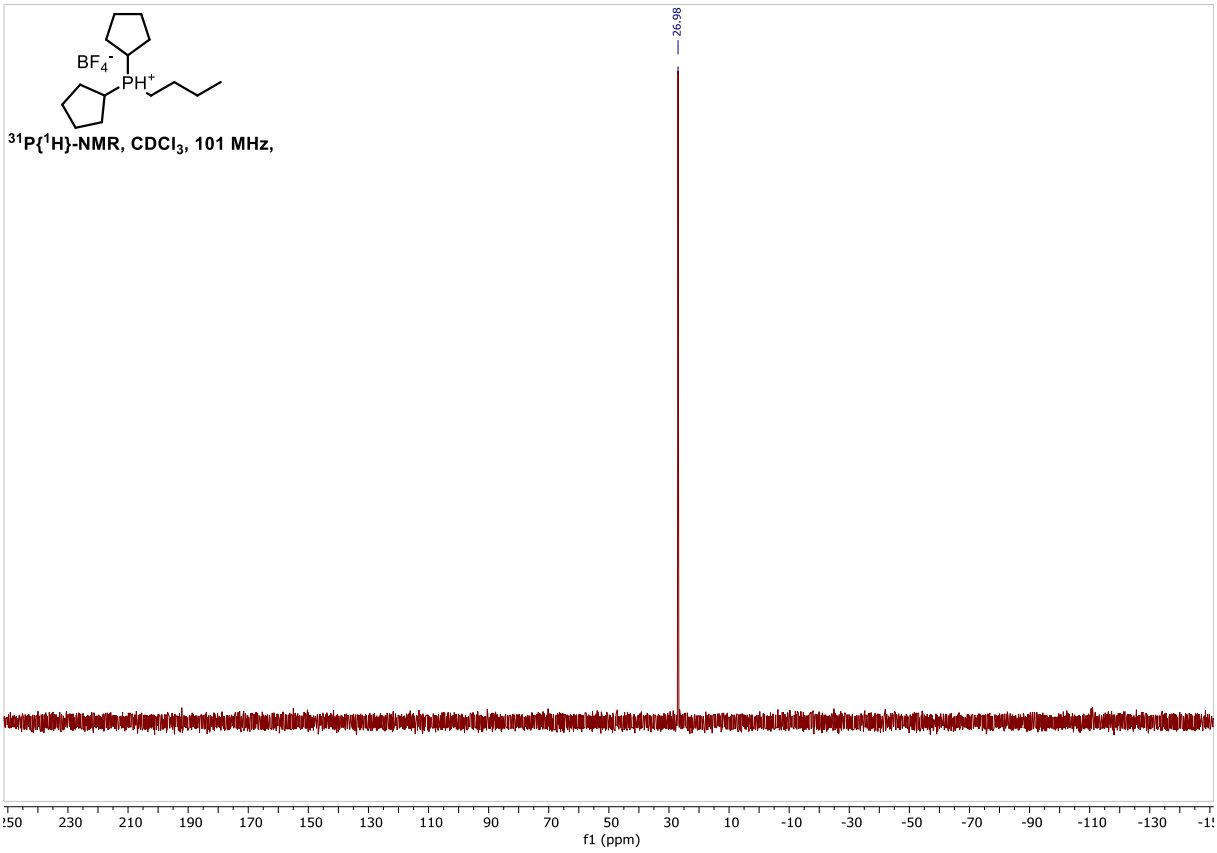




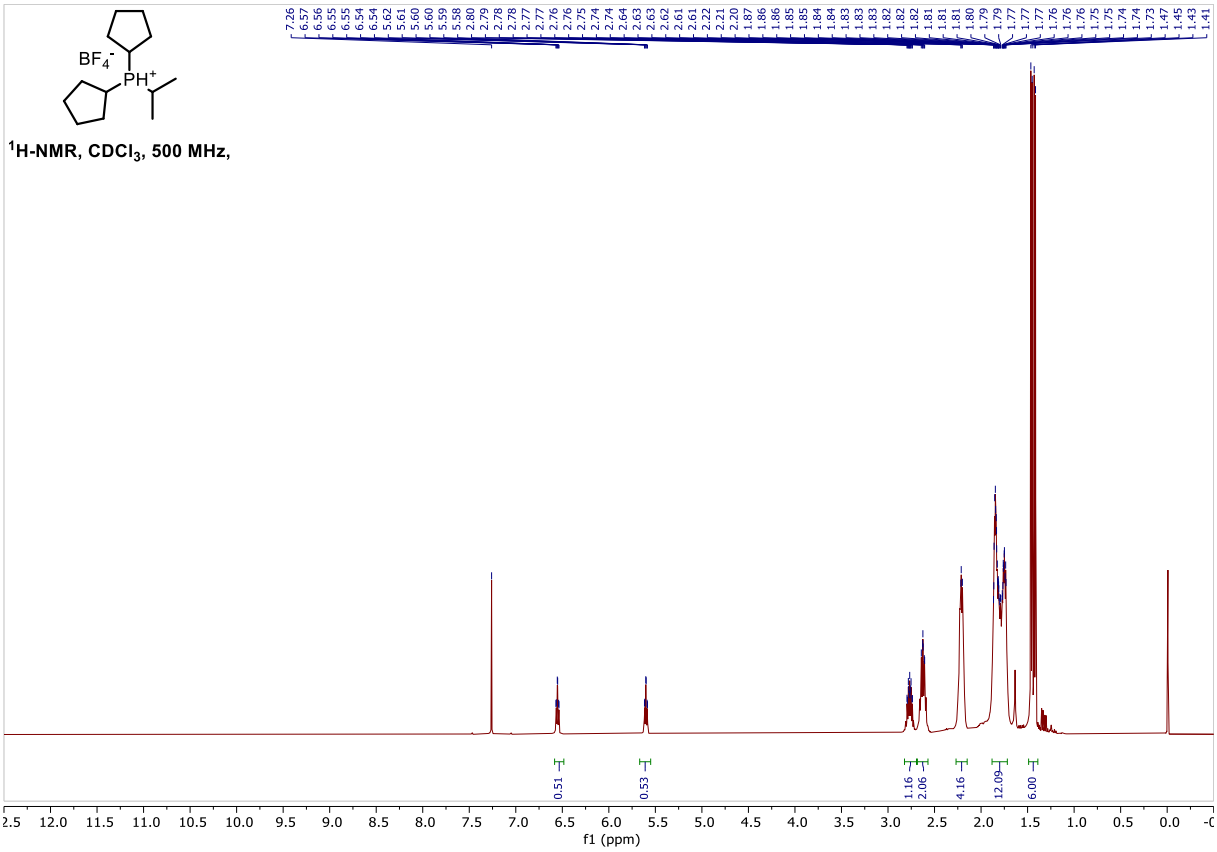
Butyldicyclopentylphosphine tetrafluoroborate (**L2.56**)

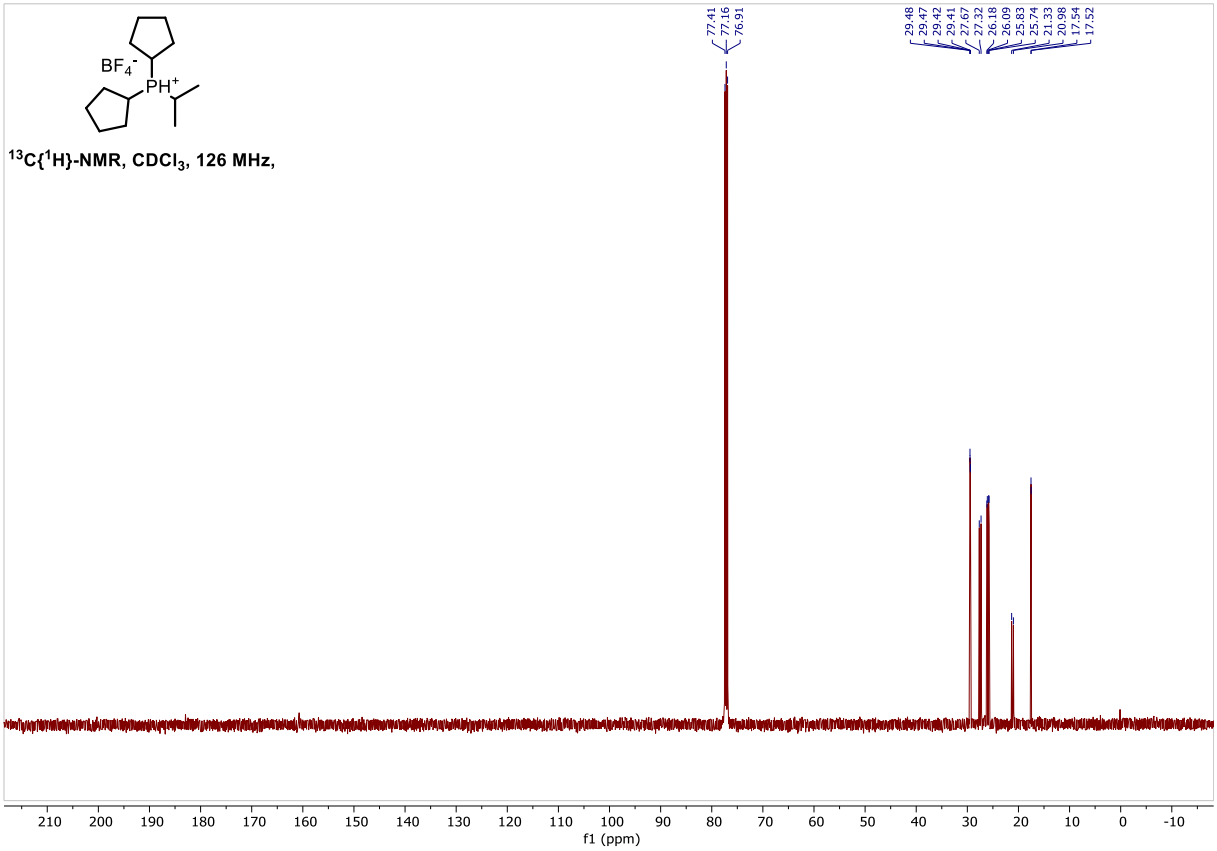


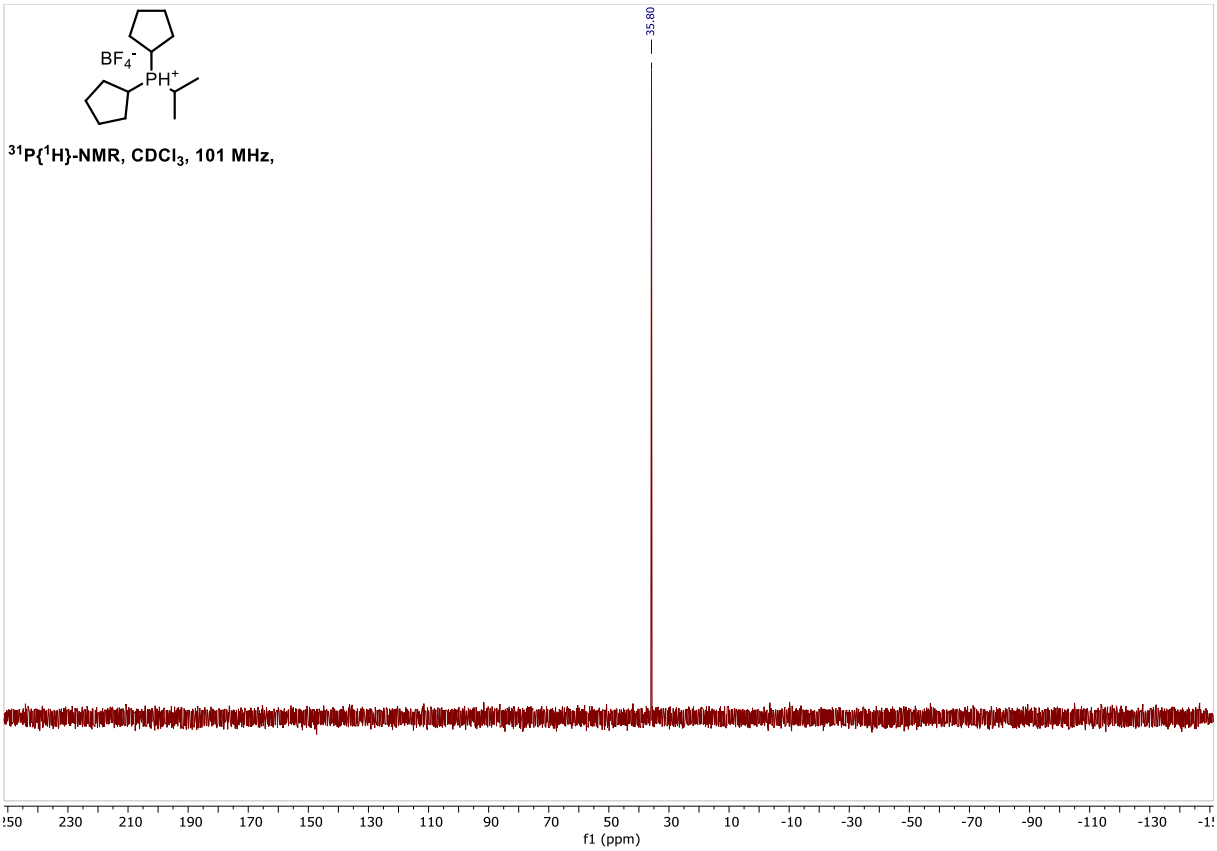

BF4-
PH+
13C{1H}-NMR, CDCl3, 126 MHz,
77.41
77.16
76.91
29.15
29.14
28.72
28.71
28.58
28.21
26.27
26.18
26.04
25.96
25.64
25.60
24.15
24.04
16.49
16.13
13.43
f1 (ppm)


BF4-
PH+
31P{1H}-NMR, CDCl3, 101 MHz,
26.98
f1 (ppm)

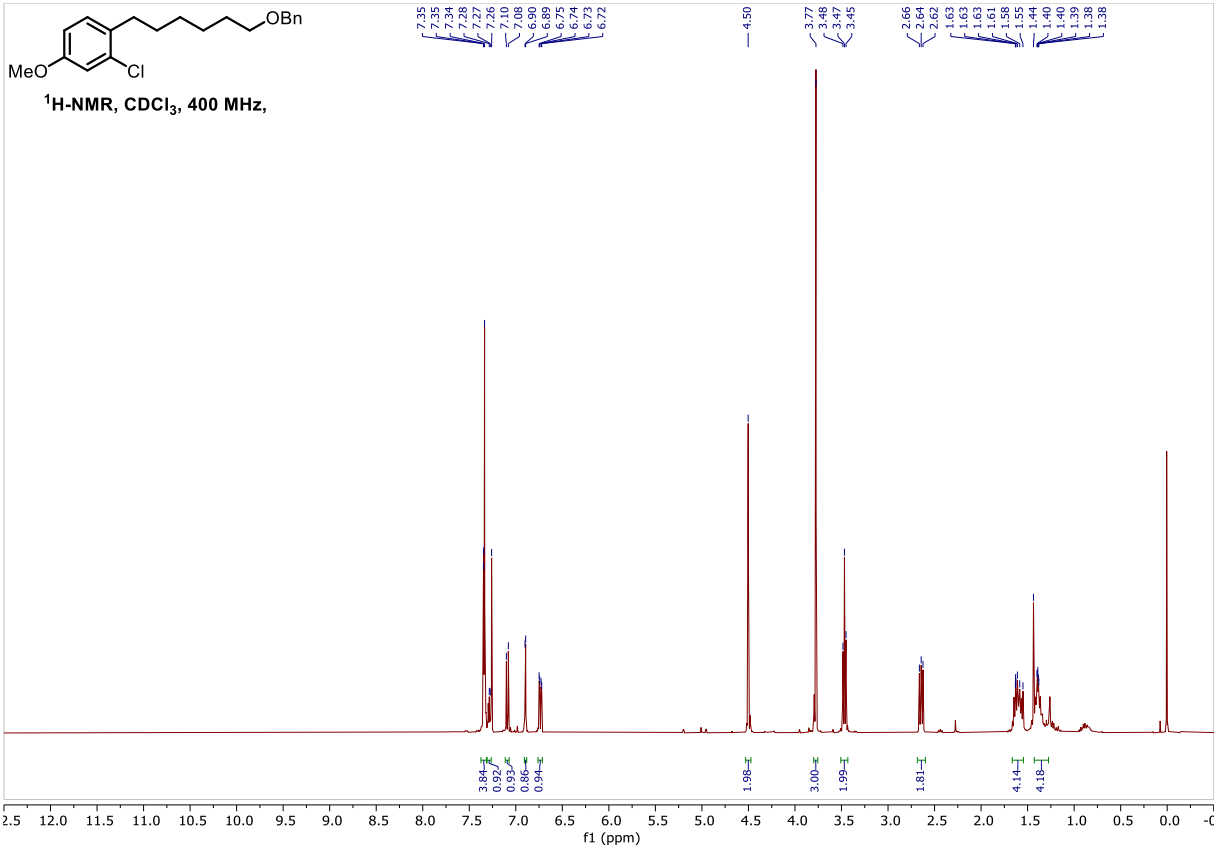
Dicyclopentyl(*iso*propyl)phosphine tetrafluoroborate (**L2.57**)

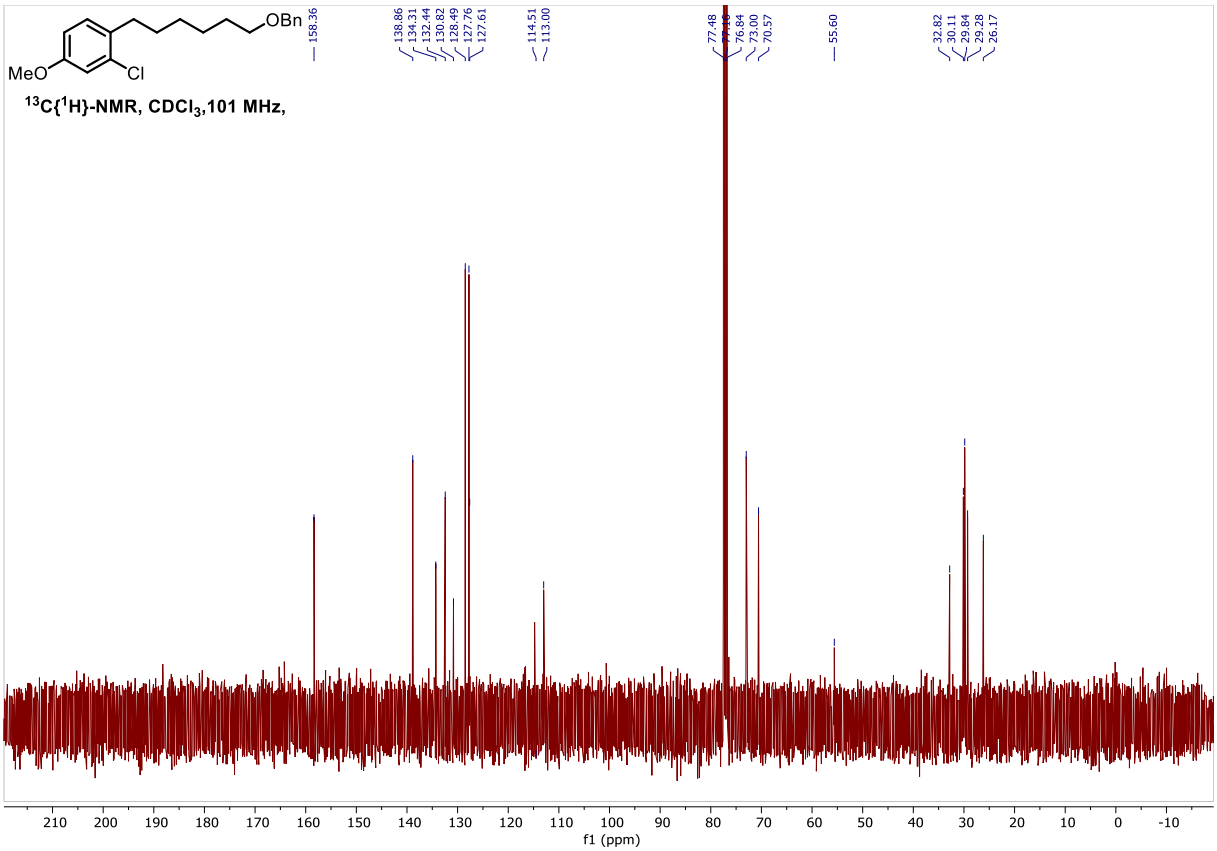




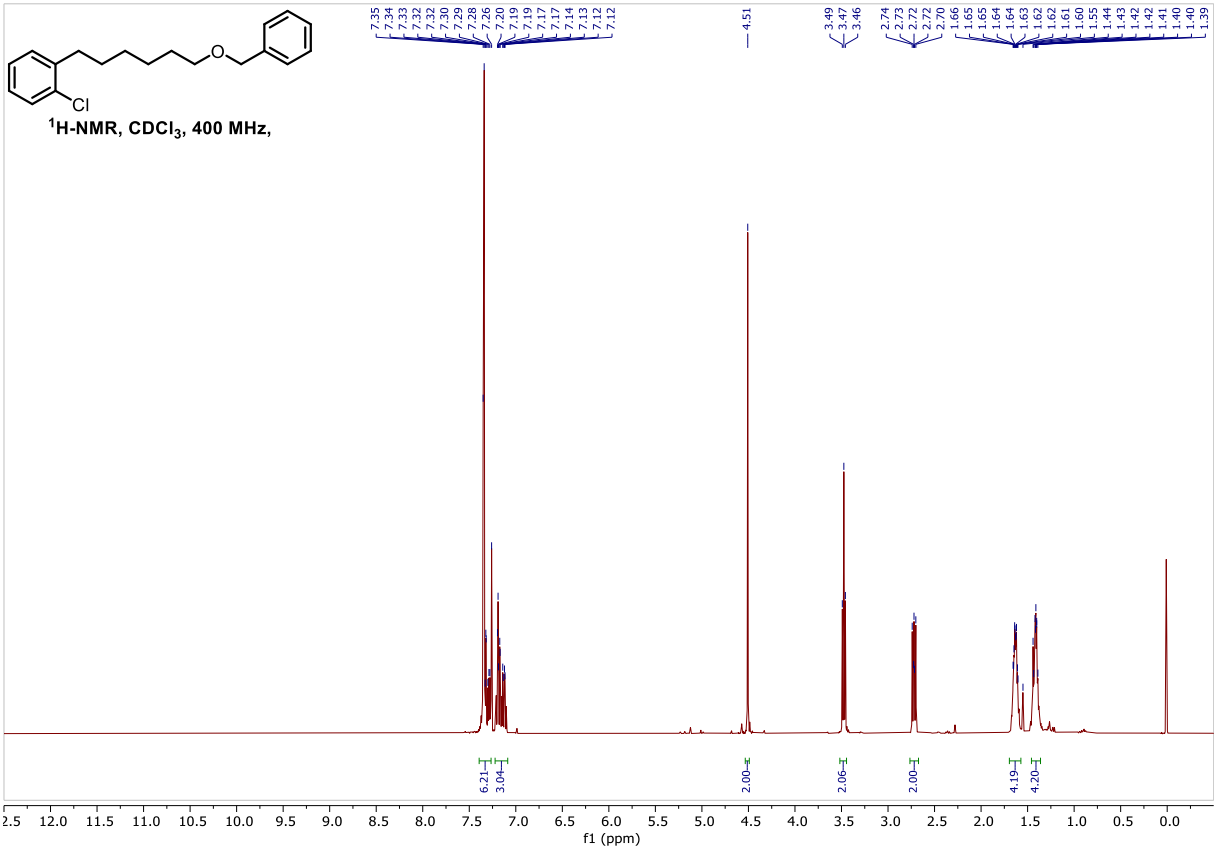


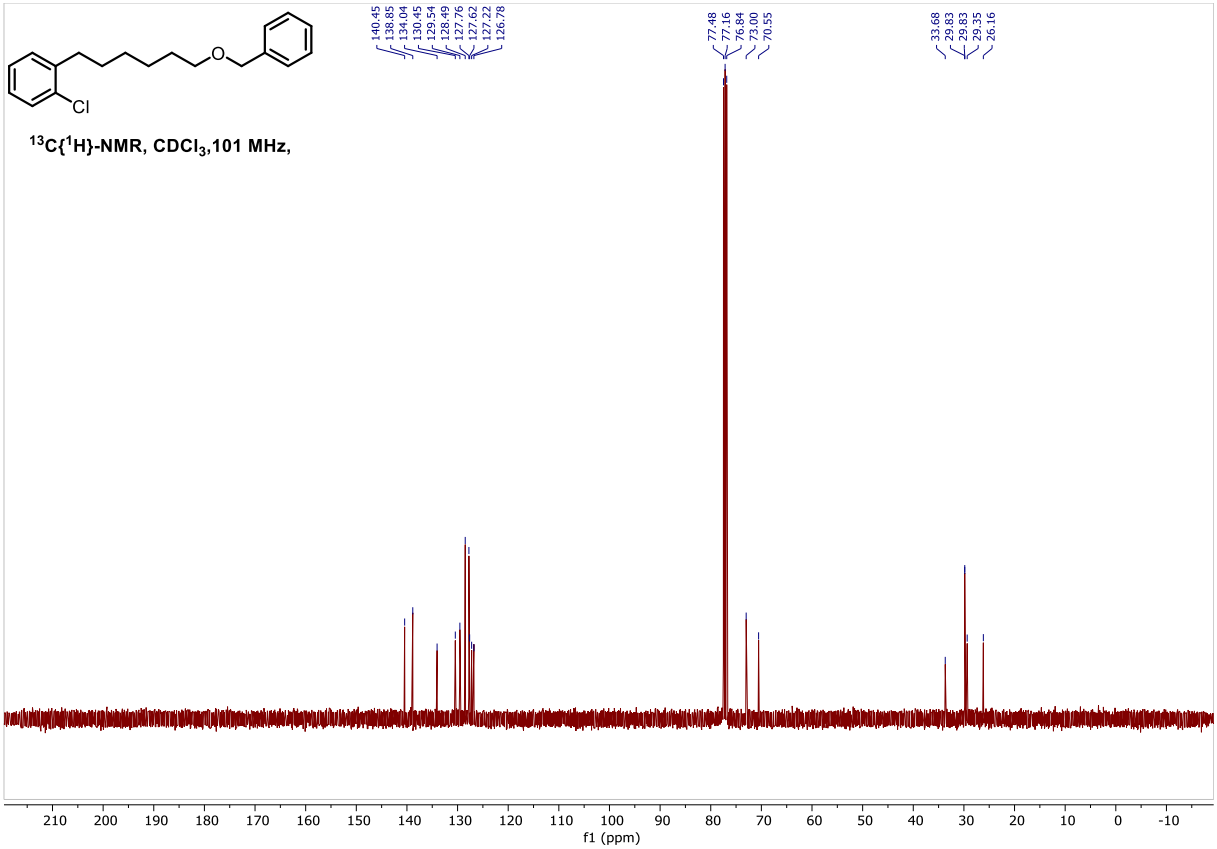
1-(6-(Benzyloxy)hexyl)-2-chloro-4-methoxybenzene (**2.3i**)



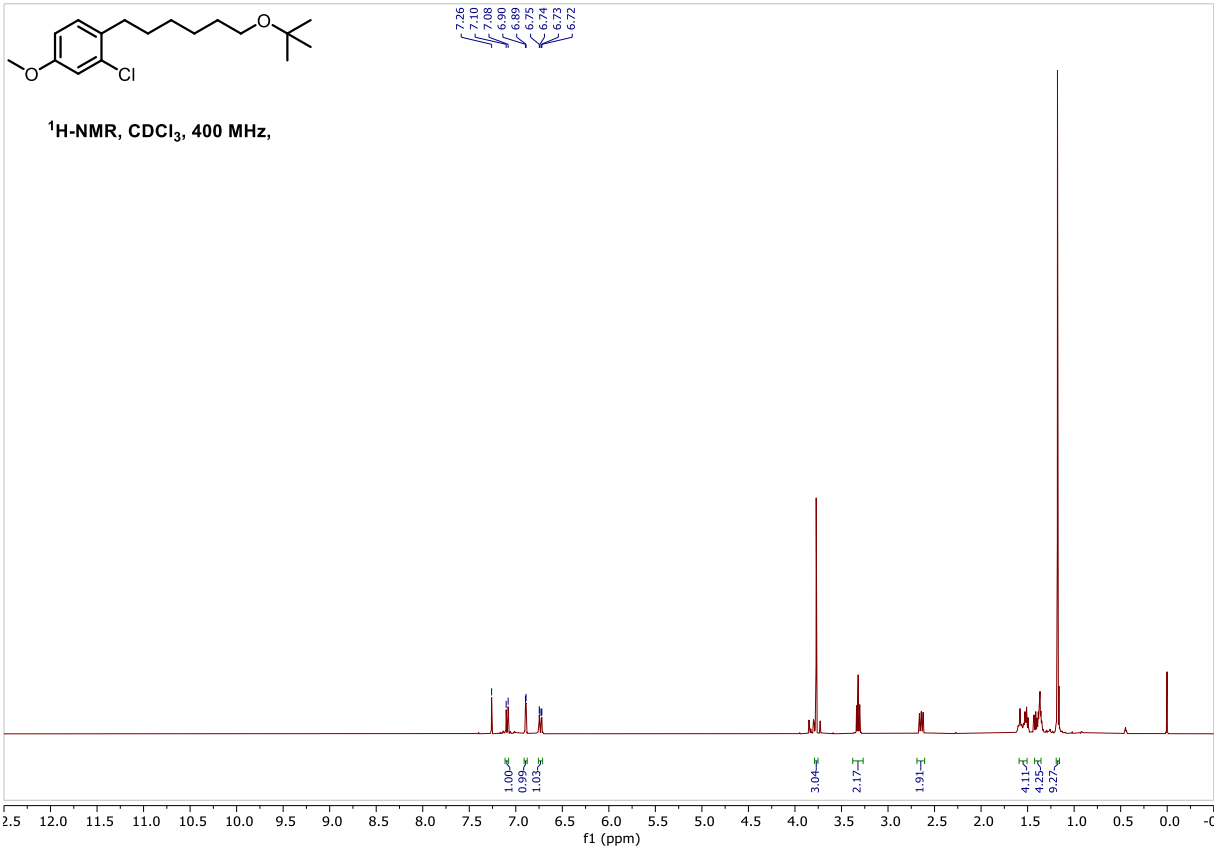


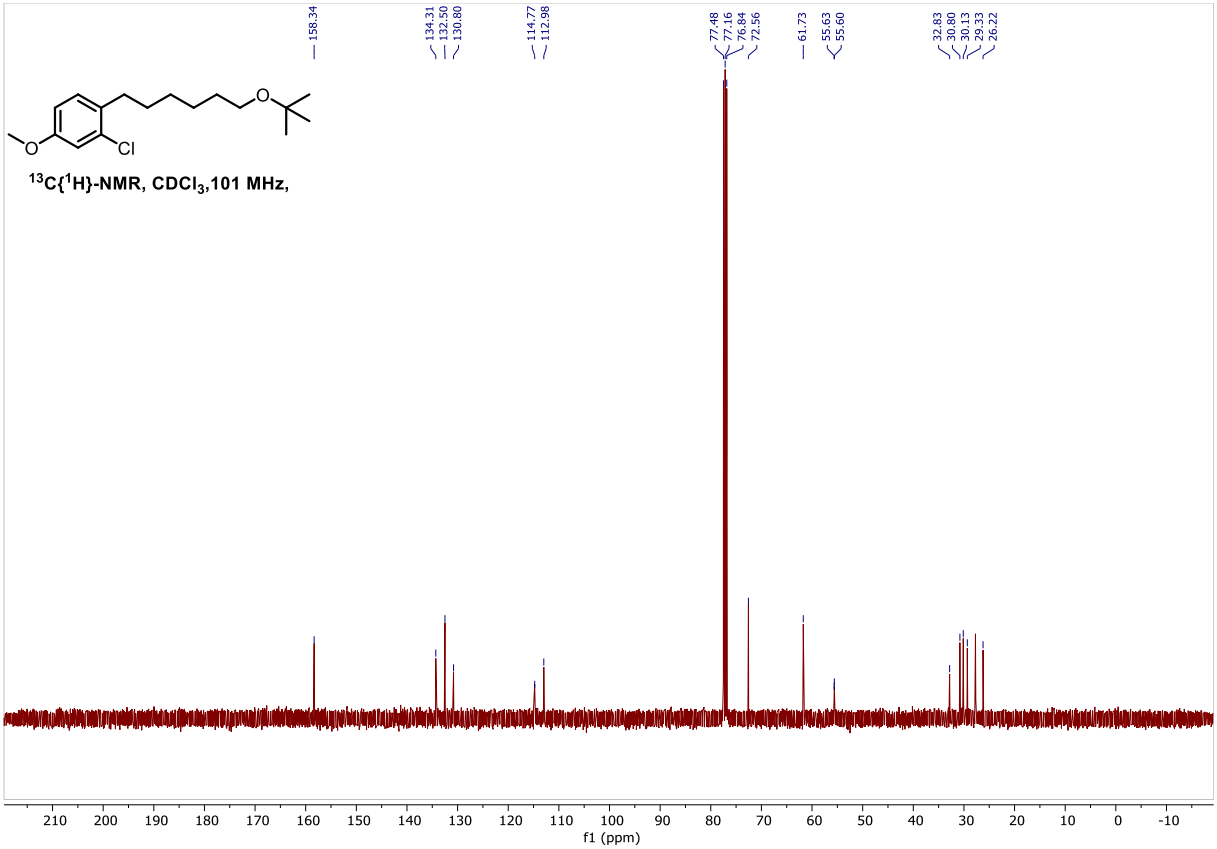
1-(6-(Benzyloxy)hexyl)-2-chlorobenzene (**2.3h**)



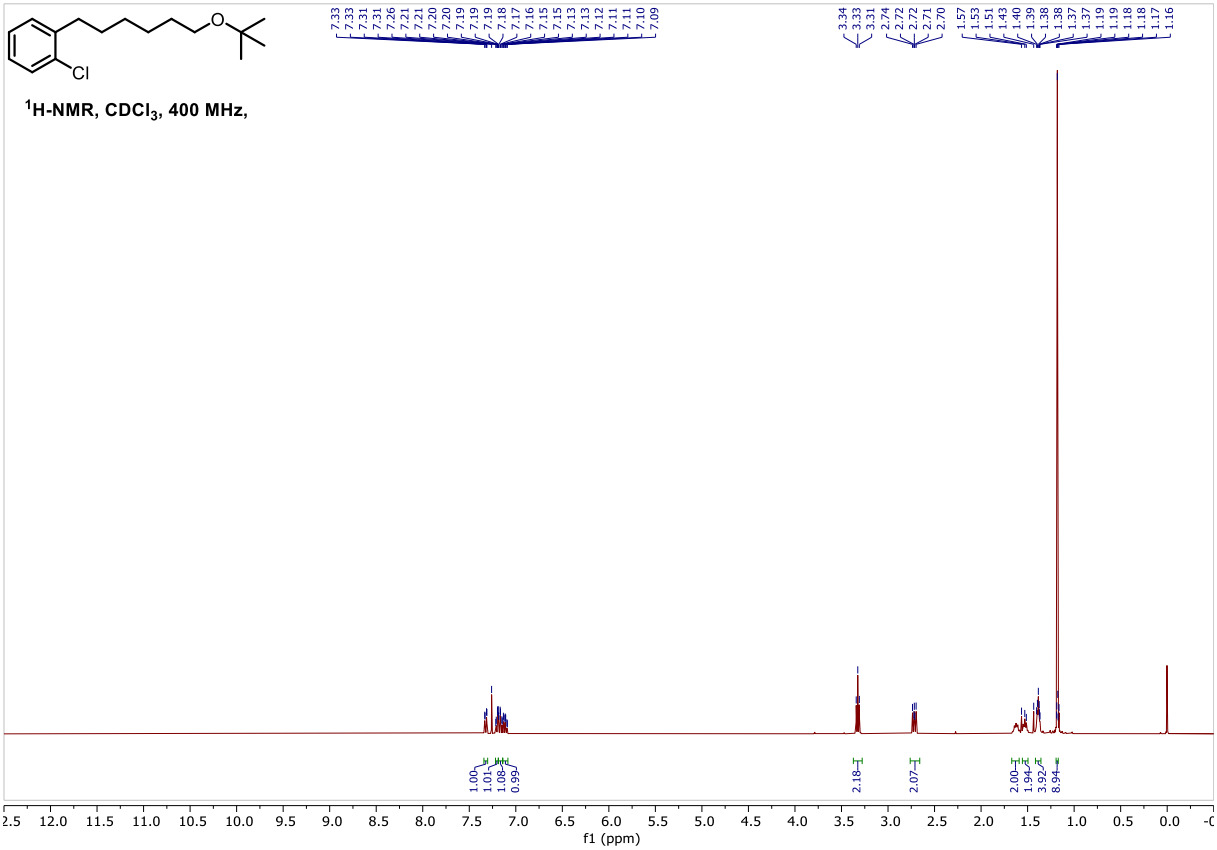


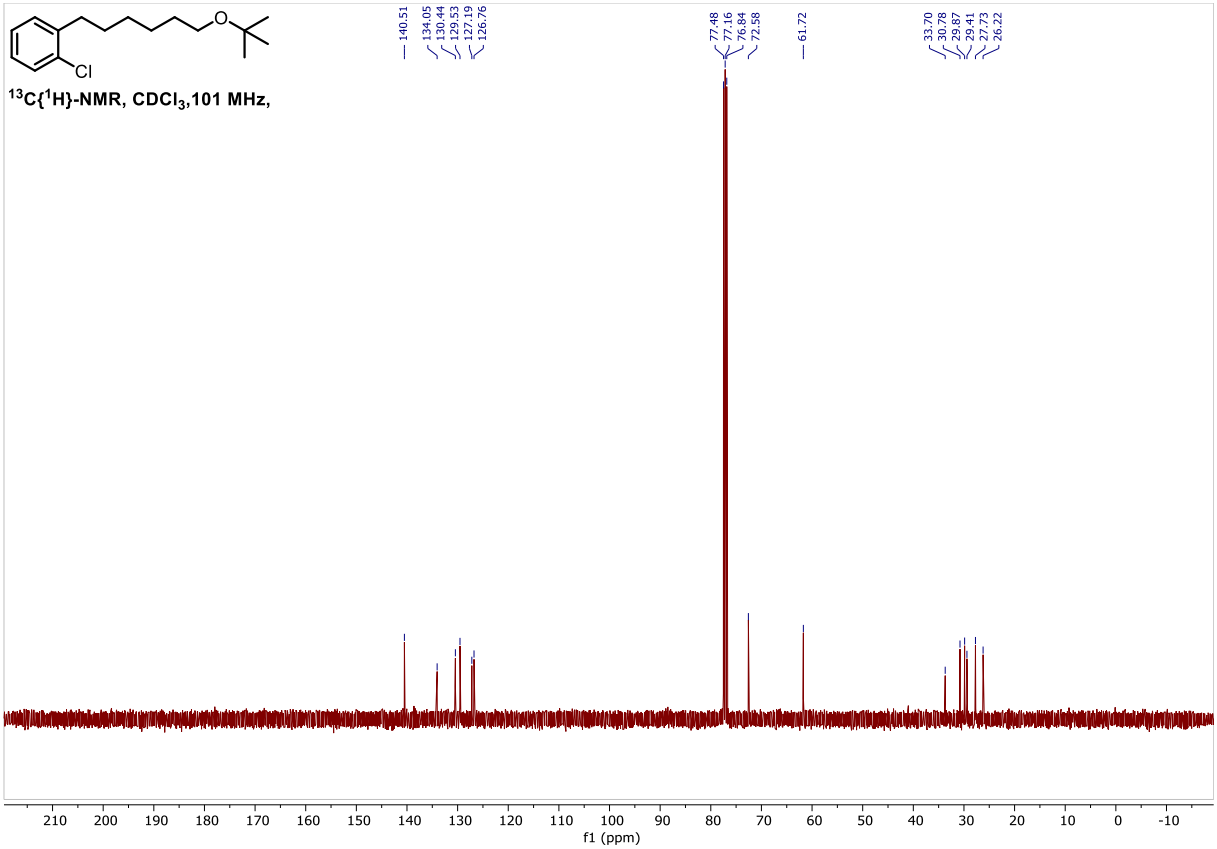
1-(6-(*tert*-Butoxy)hexyl)-2-chloro-4-methoxybenzene (**2.3i**)





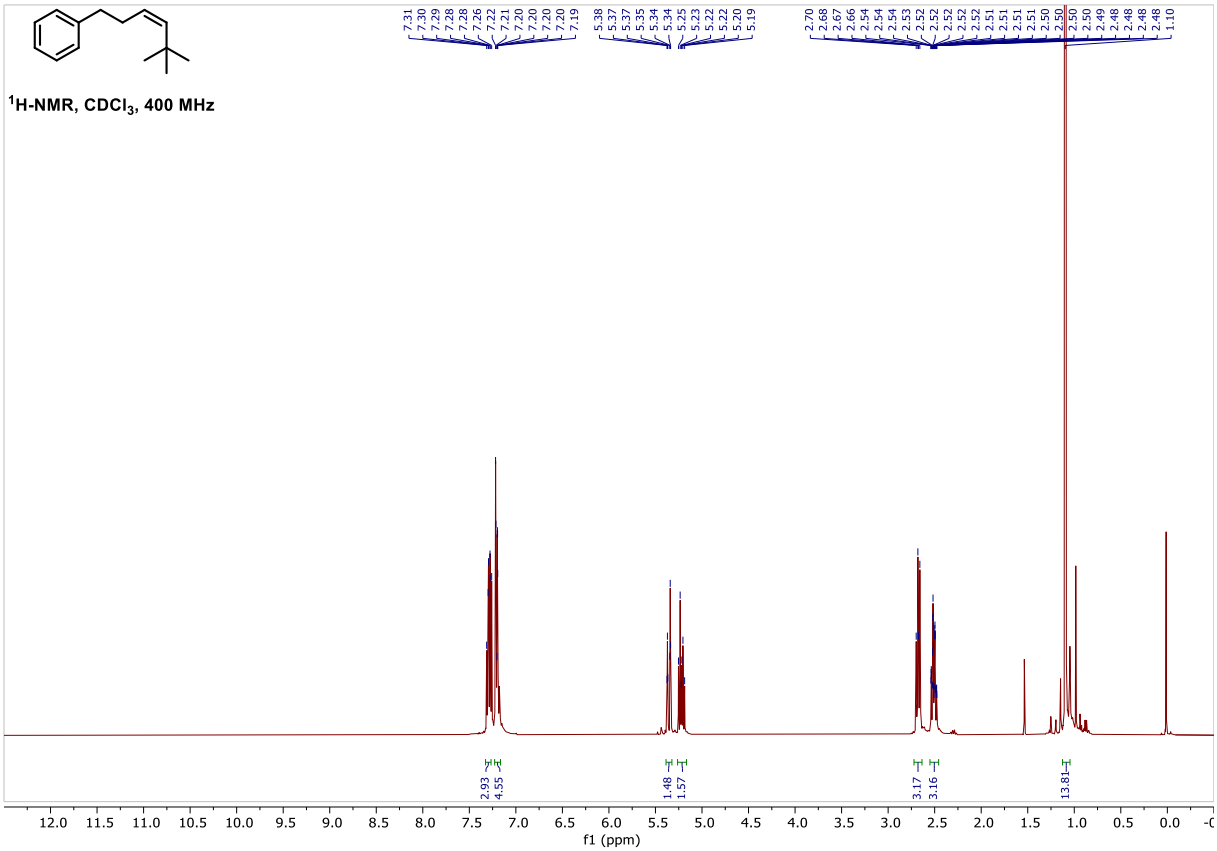
1-(6-(*tert*-Butoxy)hexyl)-2-chlorobenzene (**2.3j**)

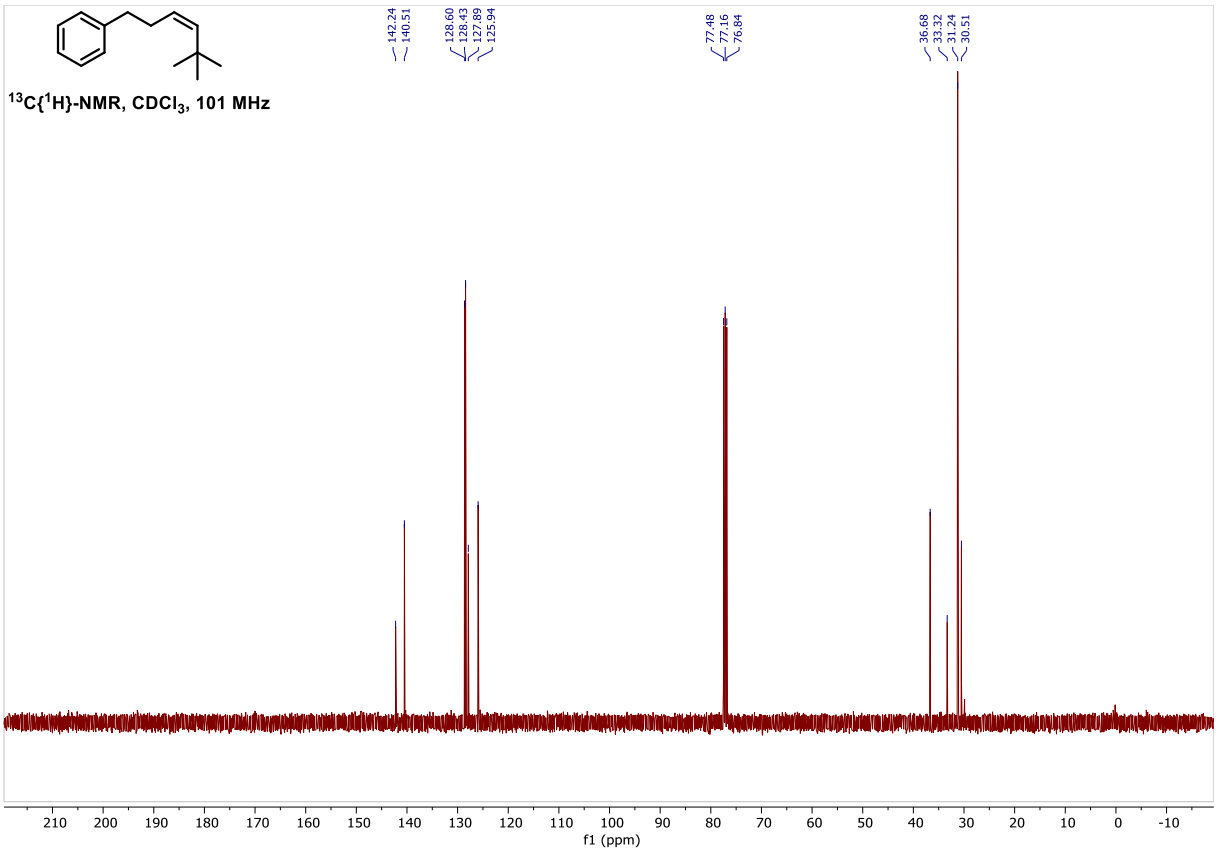




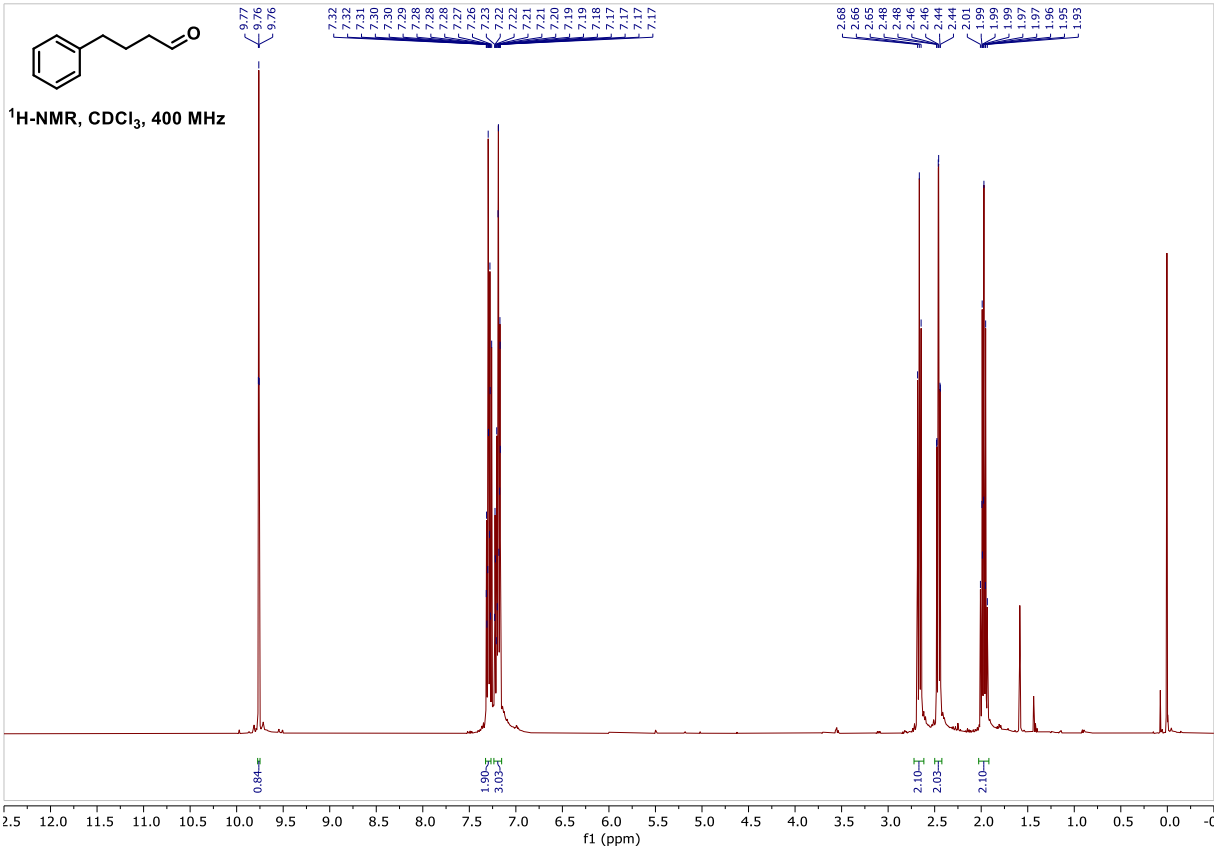
7.2. Benzylic Selective SMC

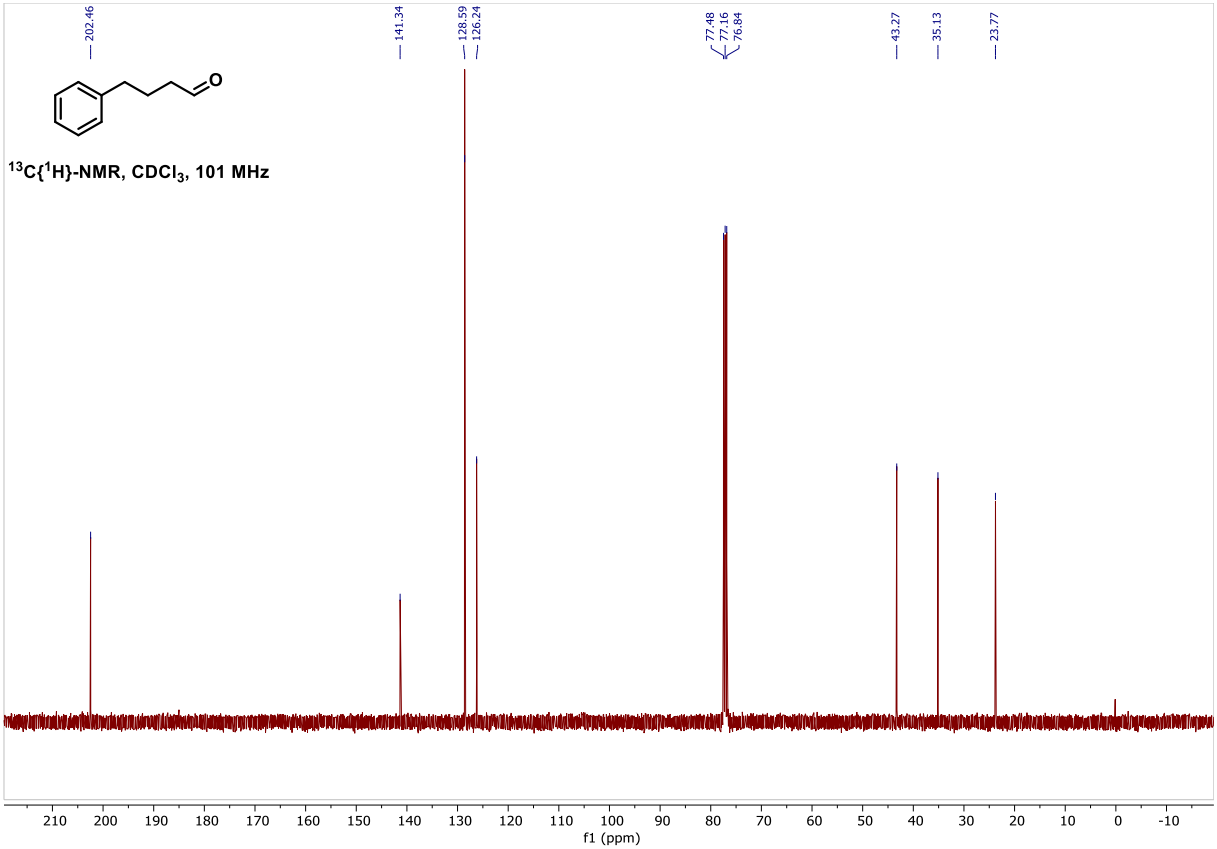
(*Z*)-(5,5-Dimethylhex-3-en-1-yl)benzene (**3.1a**)



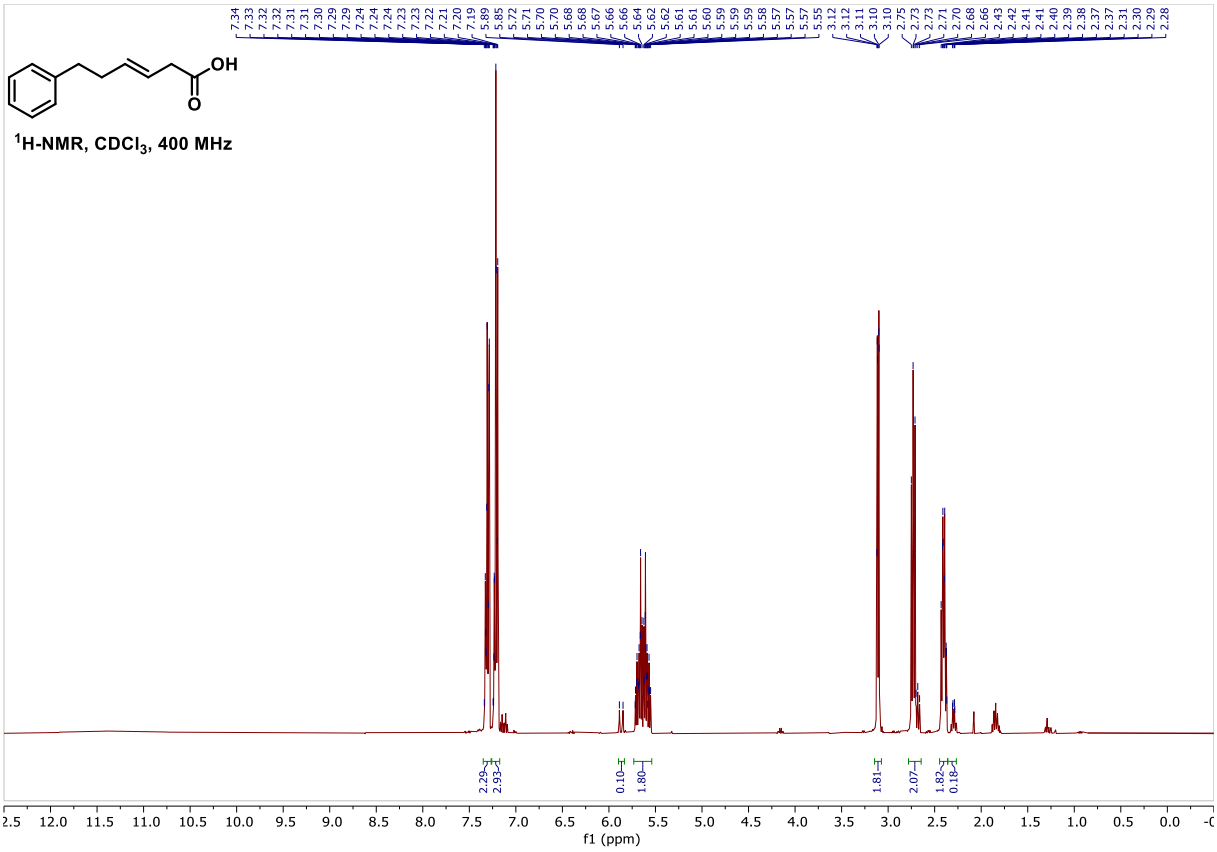


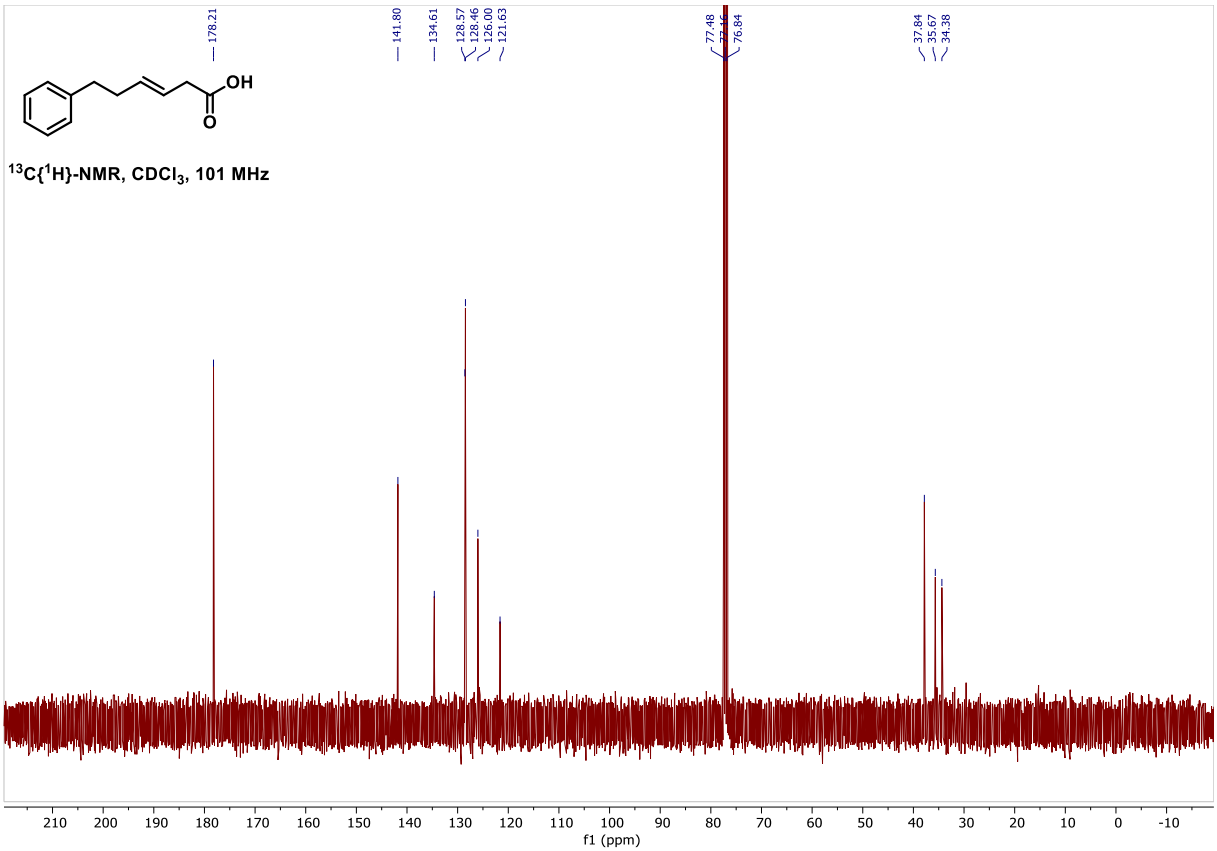
4-Phenylbutanal (**3.15**)



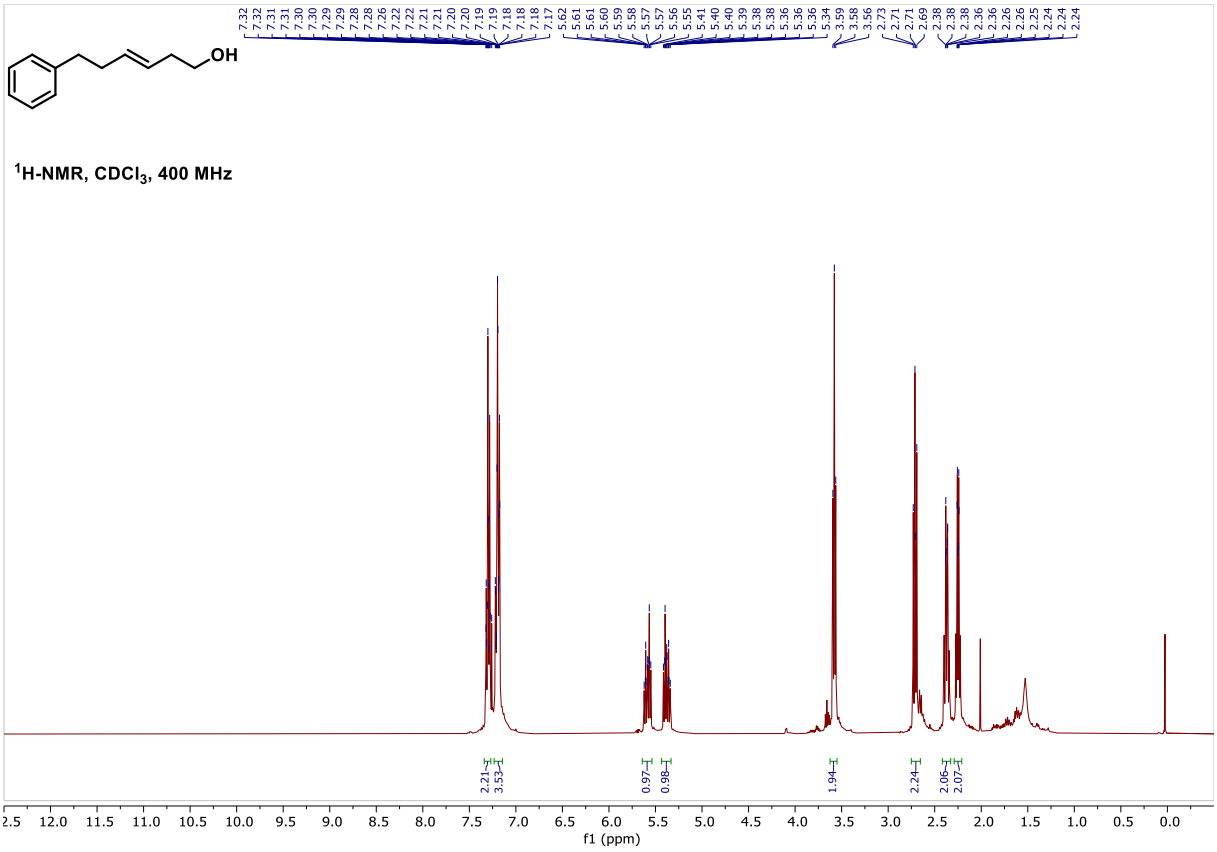


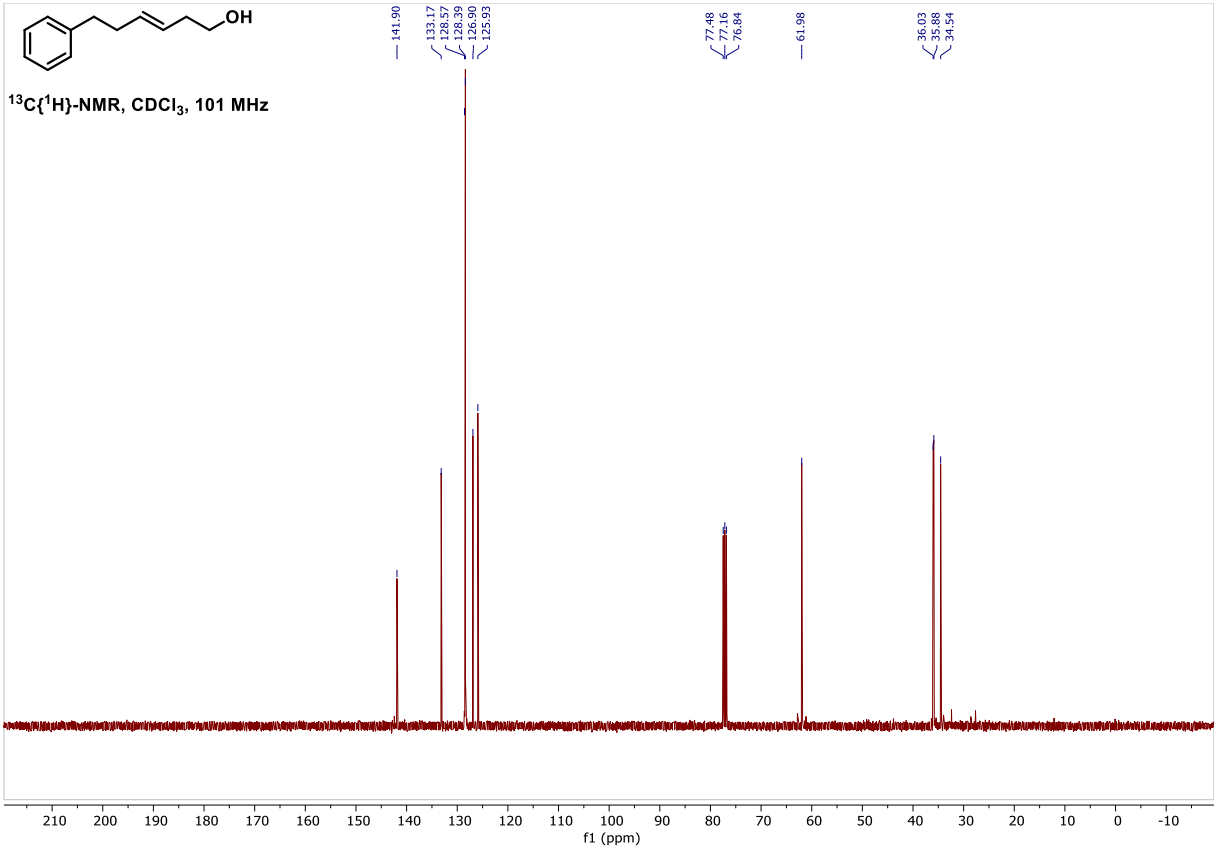
(*E*)-6-Phenyl-3-hexenoic acid (**3.16**)



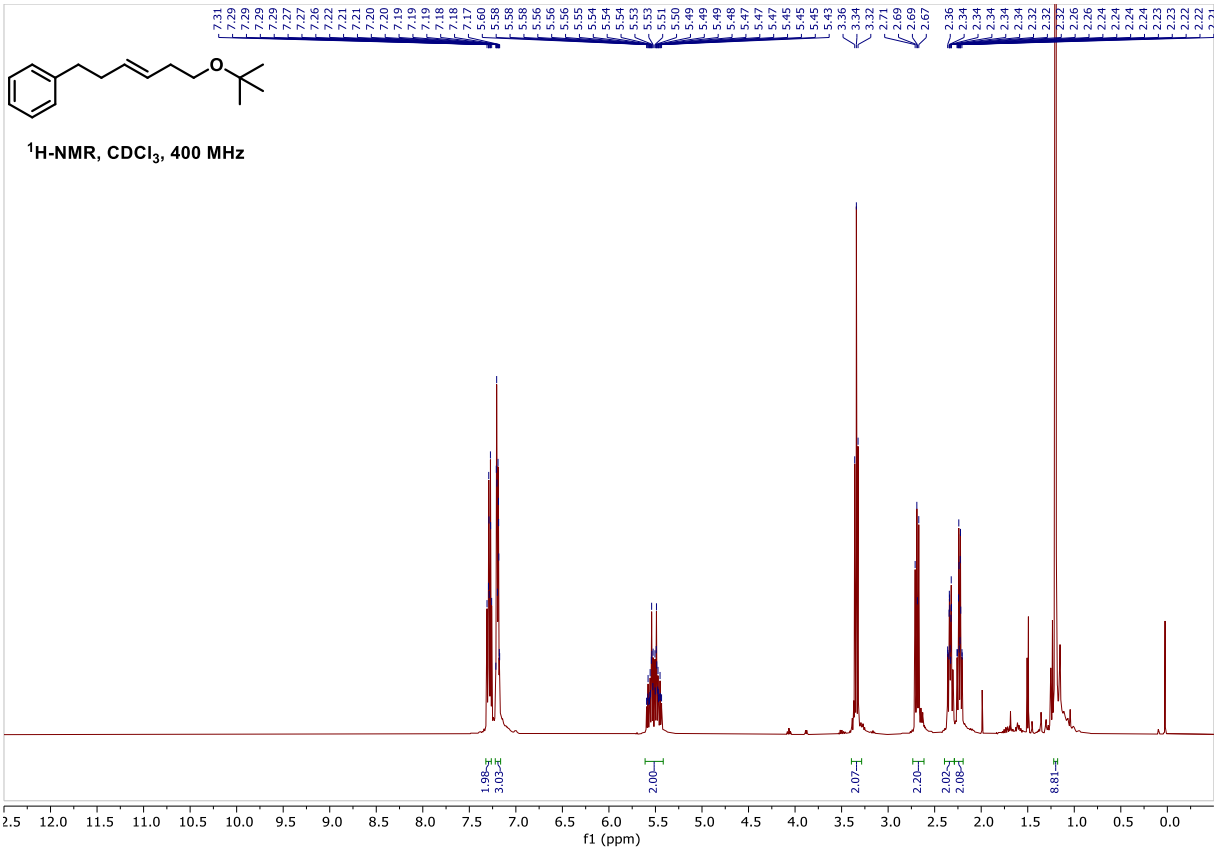


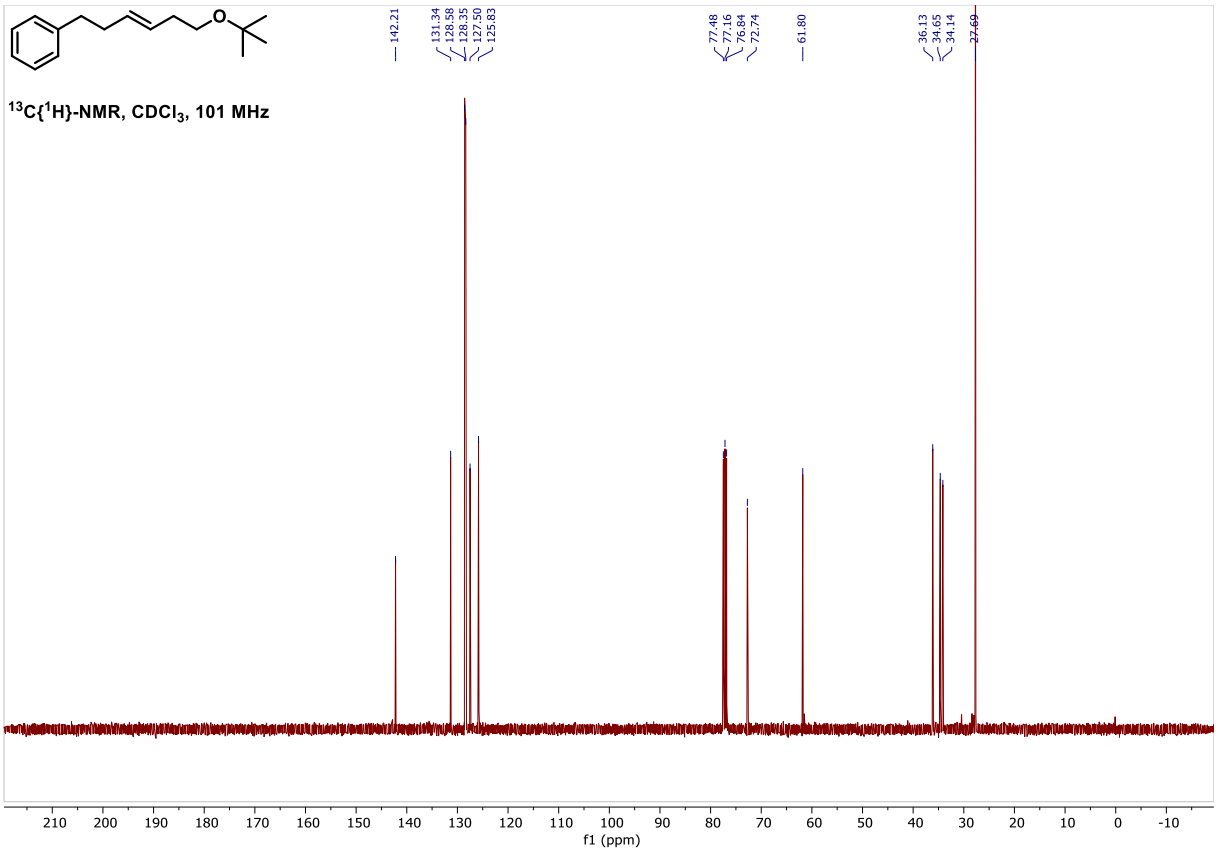
(*E*)-6-Phenyl-3-hexenol (**3.17**)



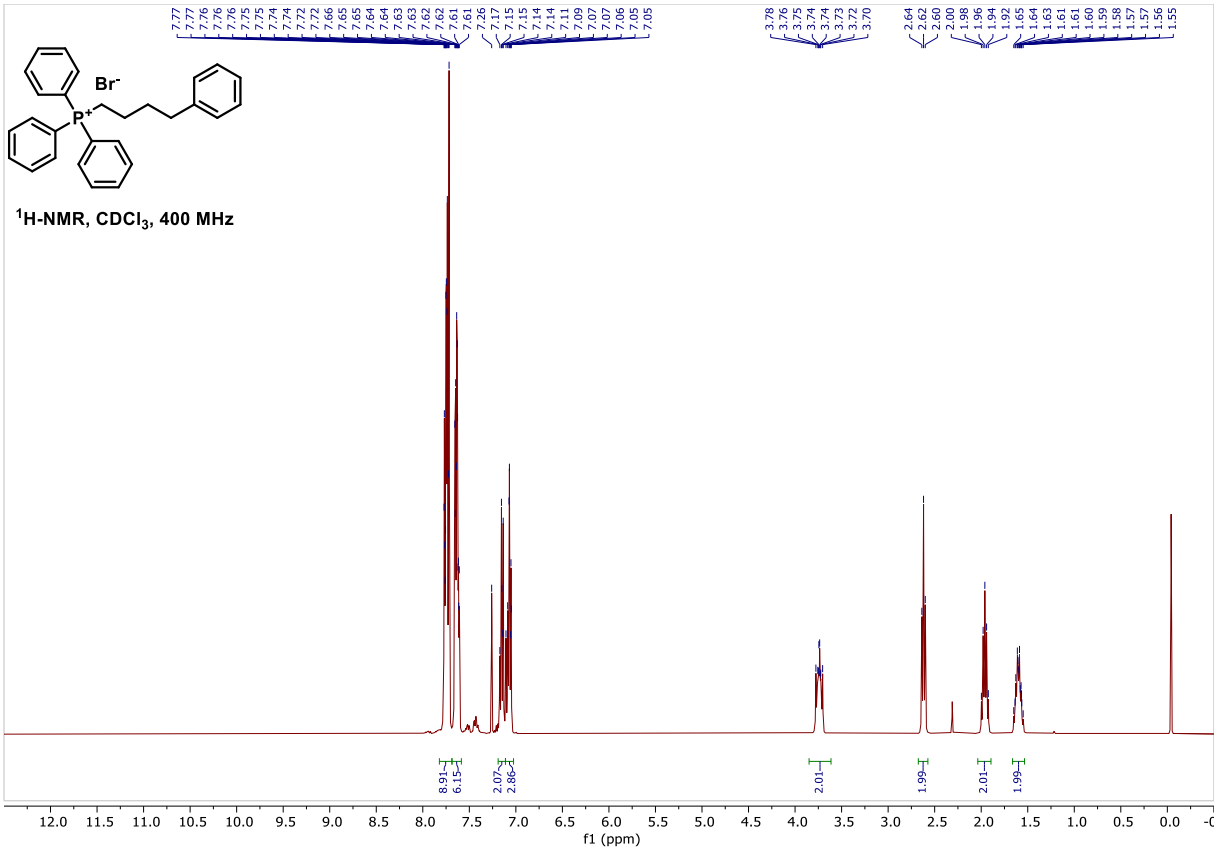


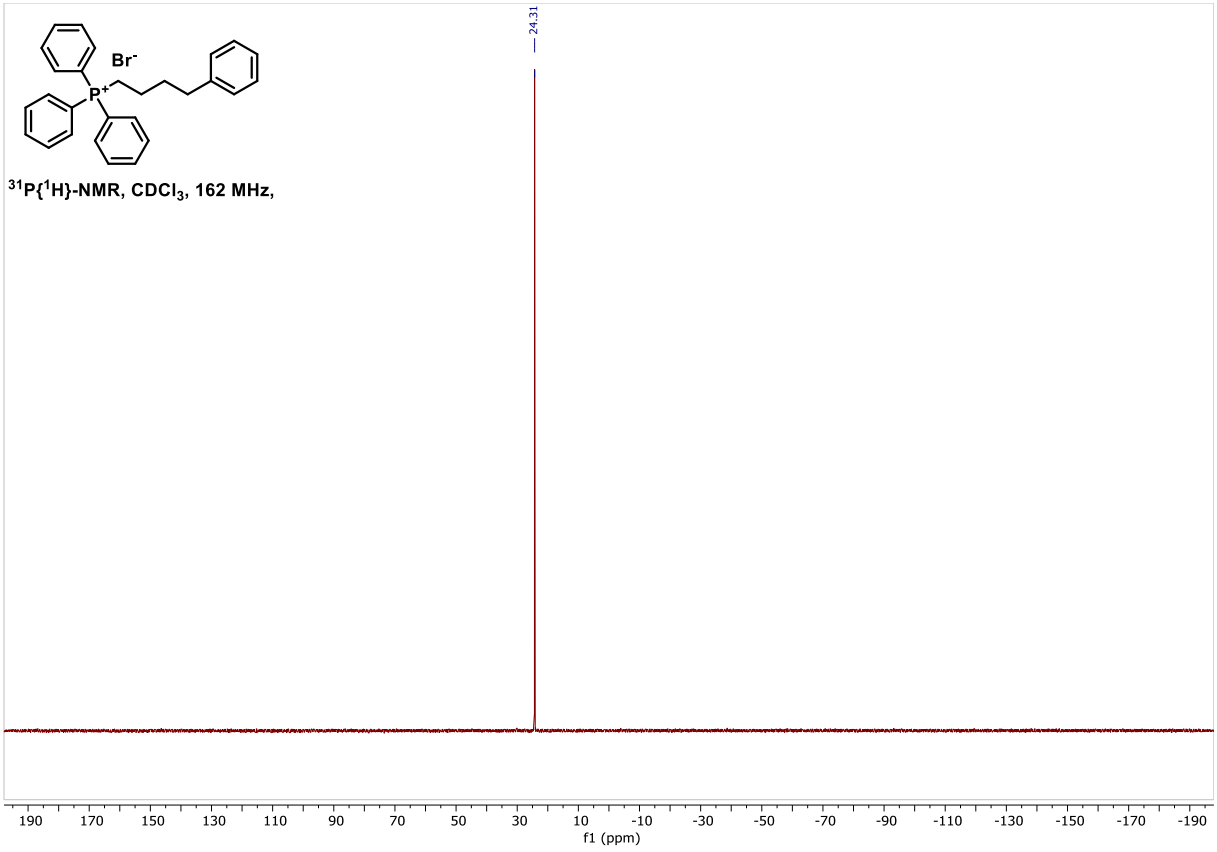
(*E*)-(6-(*tert*-Butoxy)hex-3-en-1-yl)benzene (**3.1b**)

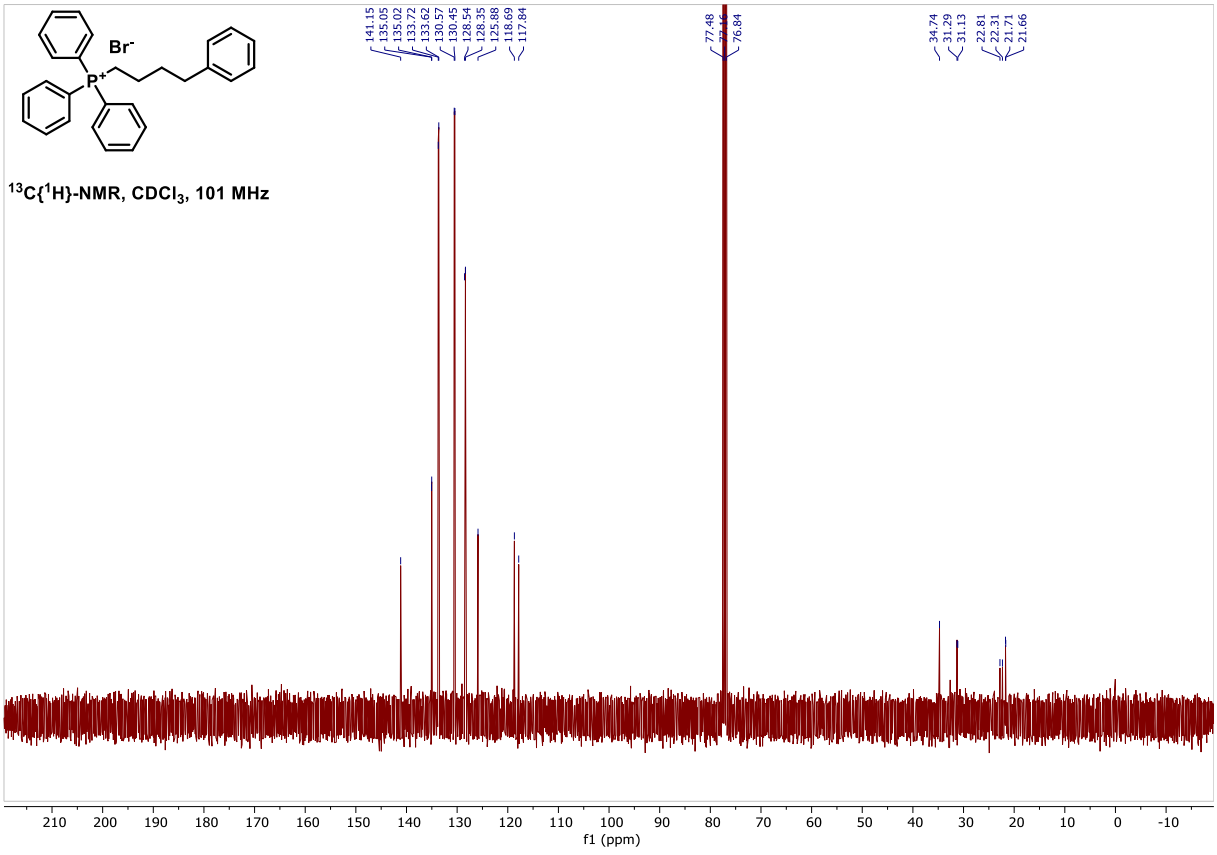




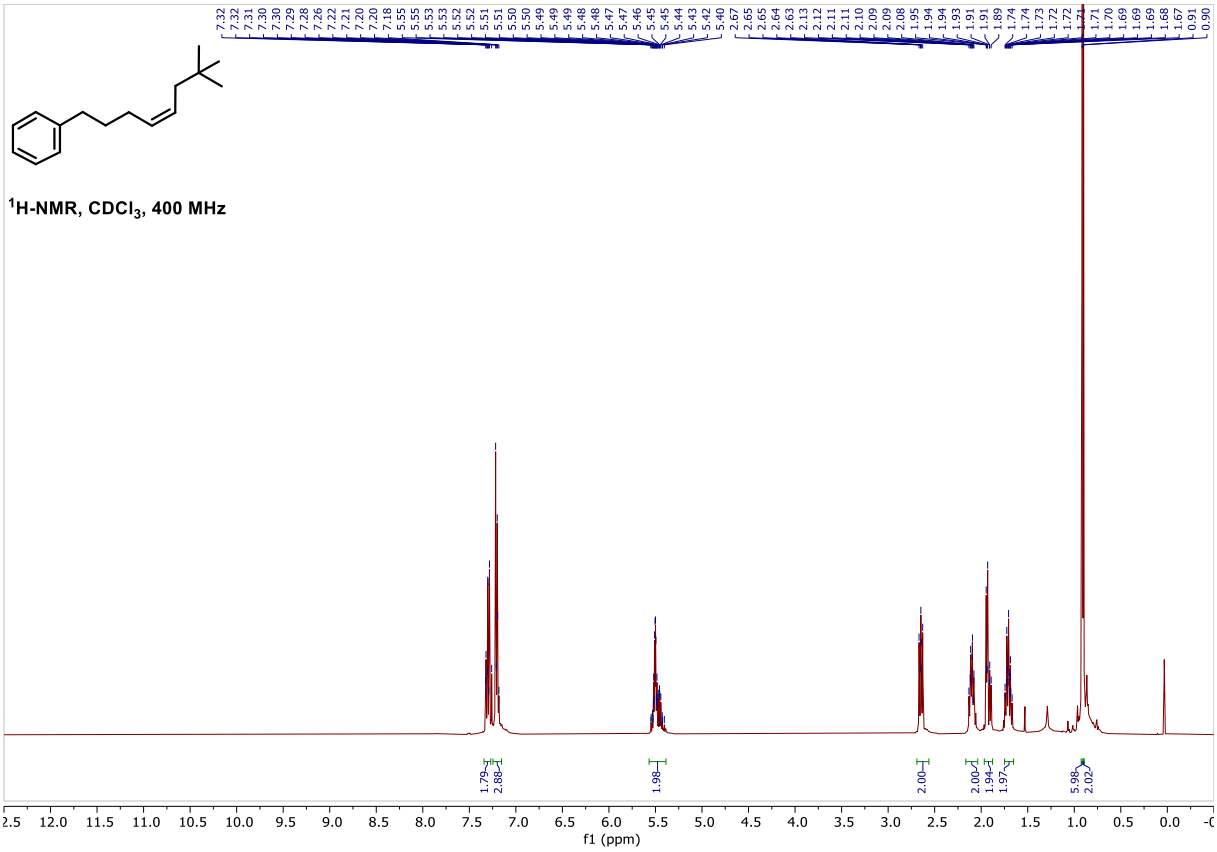
(4-Phenylbutyl)-triphenylphosphonium bromide (**3.13b**)

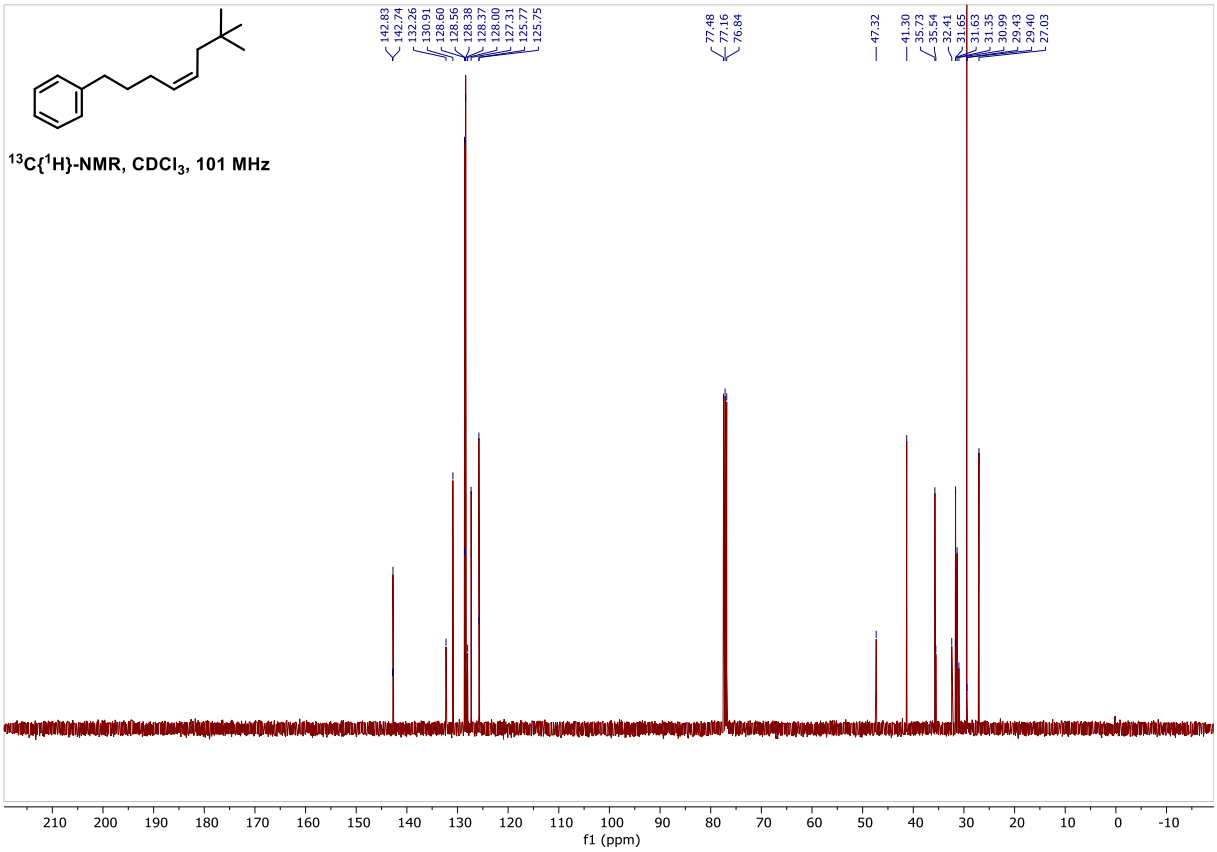



Br-
P+
24.31
31P{1H}-NMR, CDCl3, 162 MHz,
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

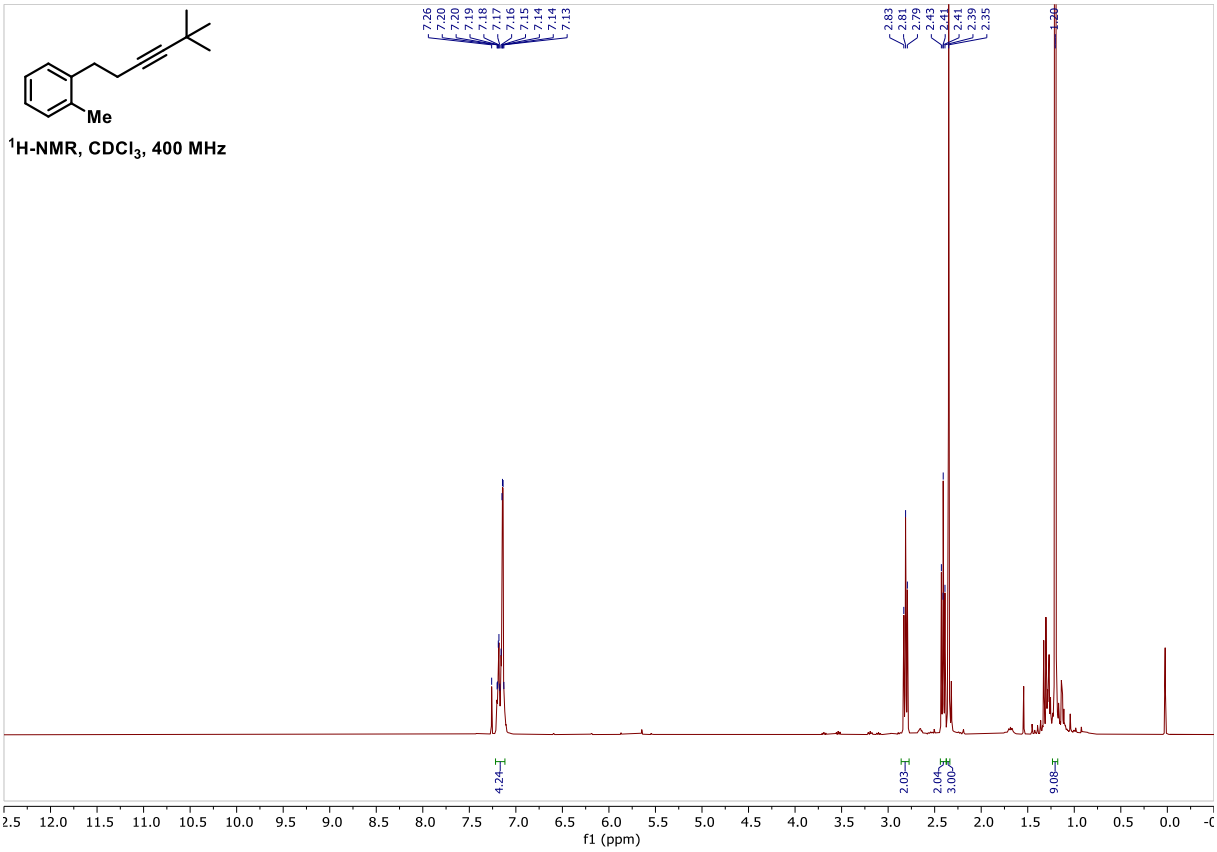

Br-
P+
141.15
135.05
135.02
133.72
133.62
130.57
130.45
128.54
128.35
125.88
118.69
117.84
77.48
77.16
76.84
34.74
31.29
31.13
22.81
22.31
21.71
21.66
13C{1H}-NMR, CDCl3, 101 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

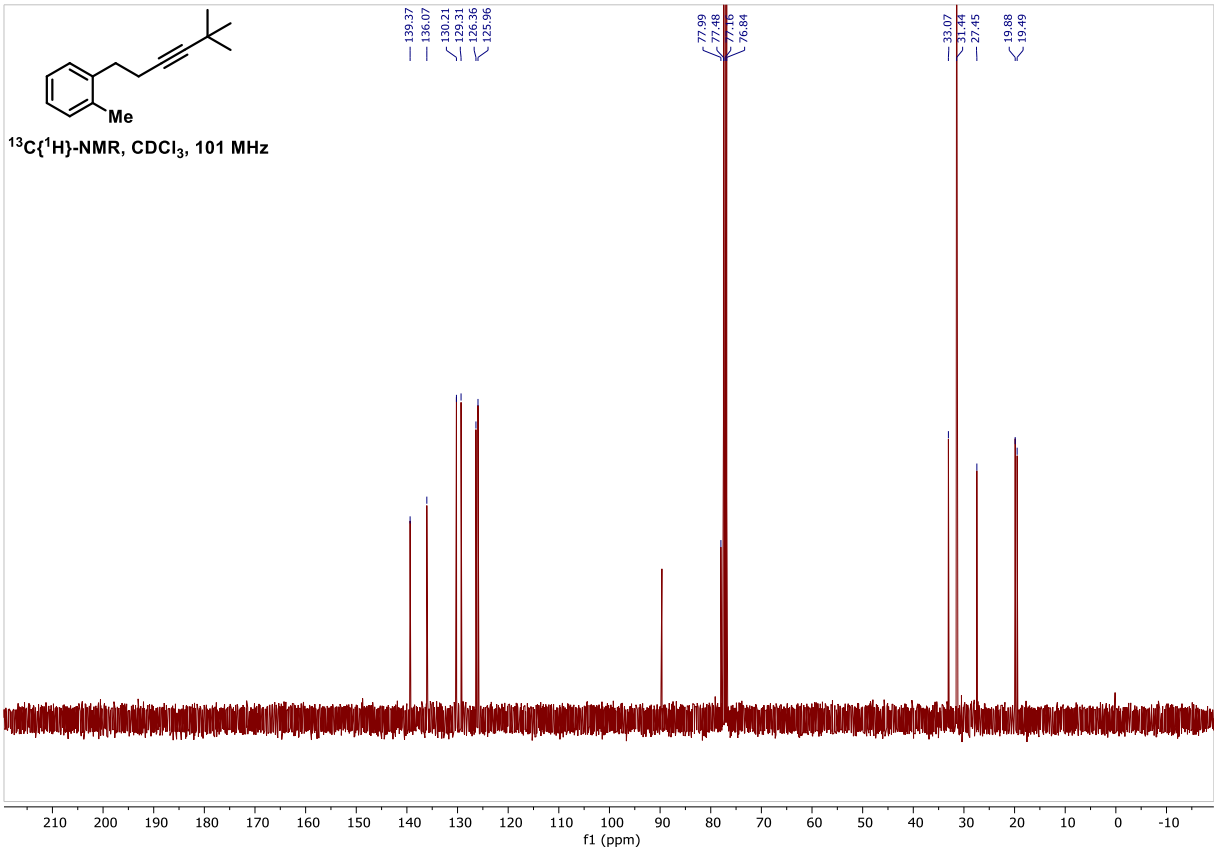
(*Z*)-(7,7-Dimethyloct-4-en-1-yl)benzene (**3.1c**)



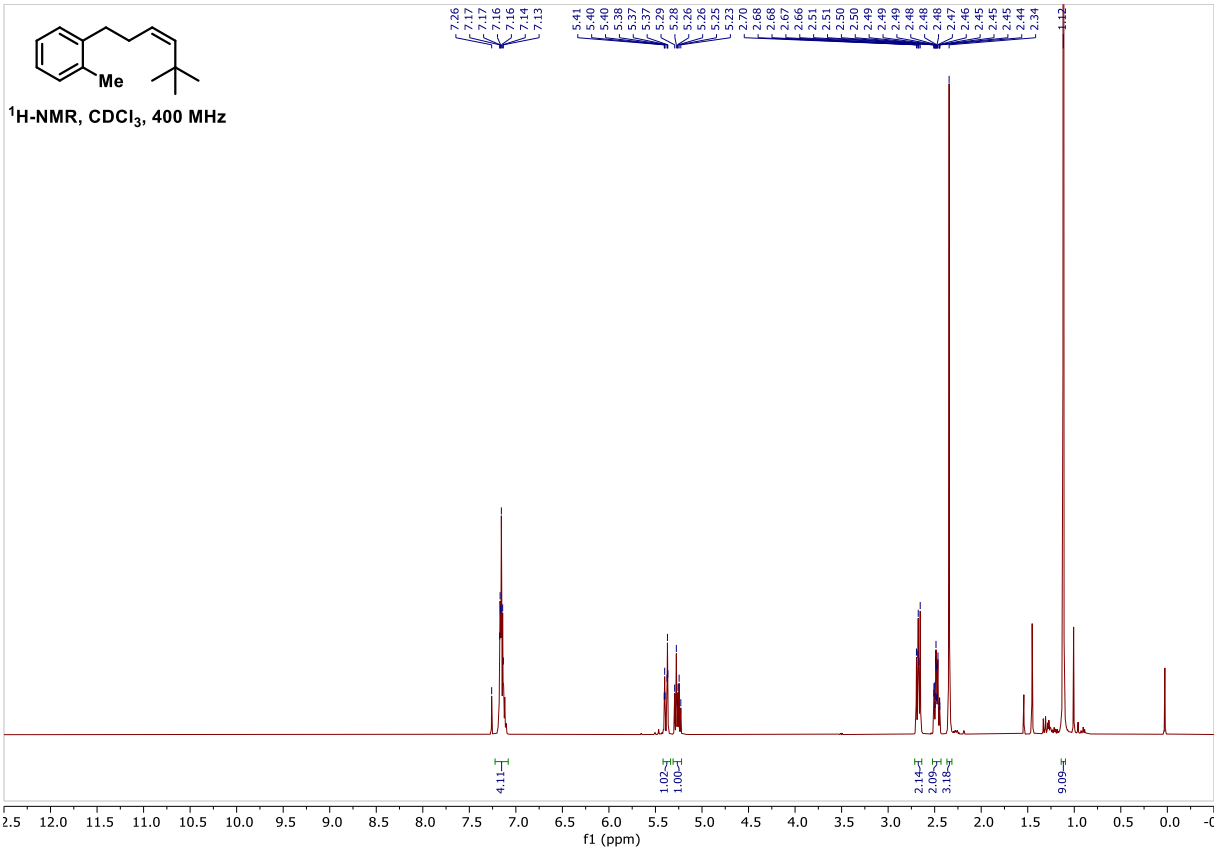


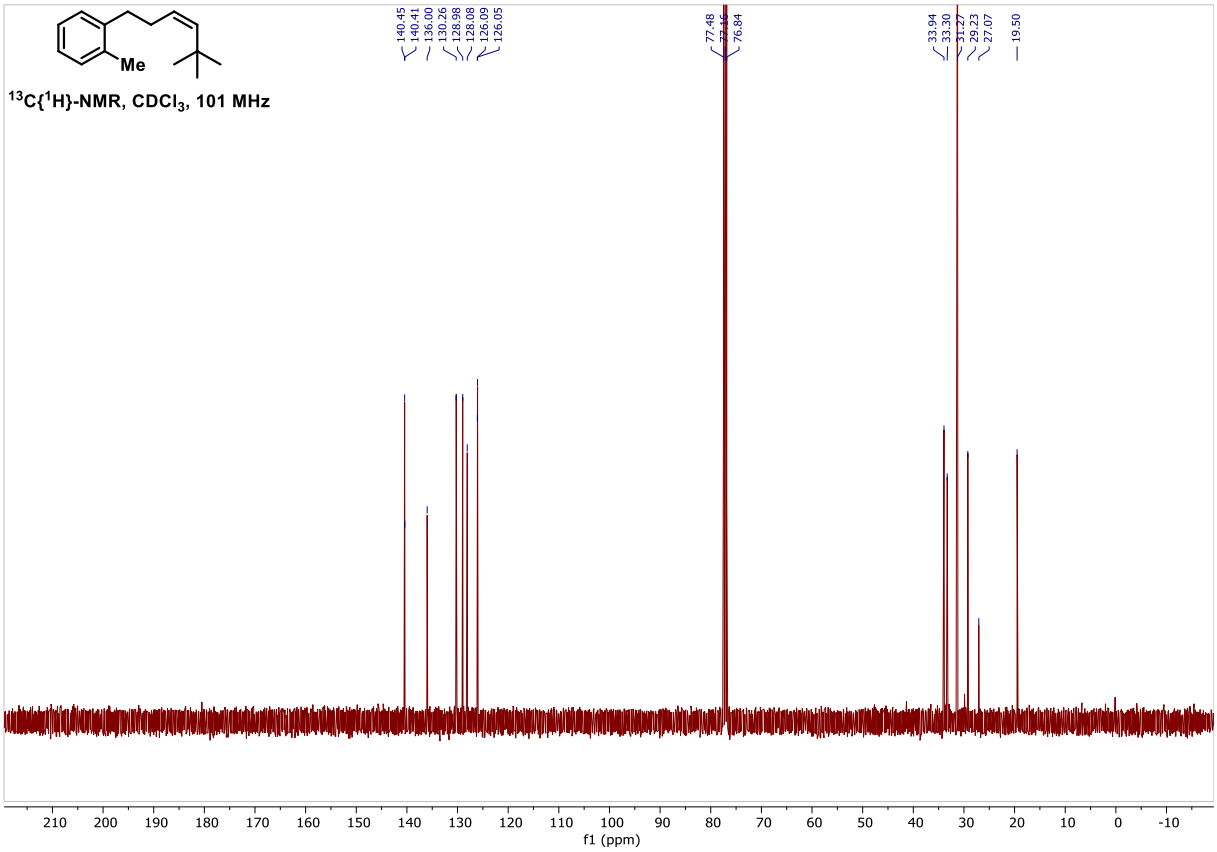
1-(5,5-Dimethylhex-3-yn-1-yl)-2-methylbenzene (**3.20a**)



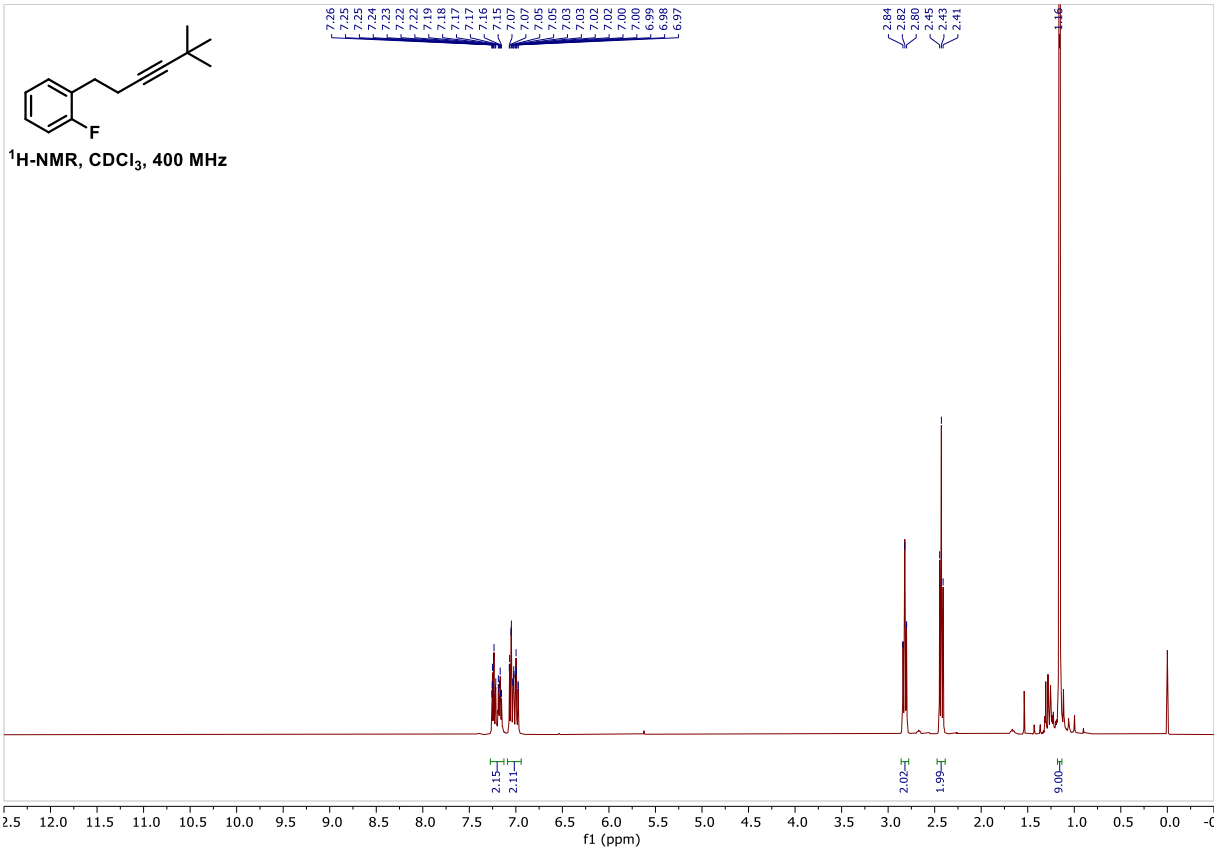


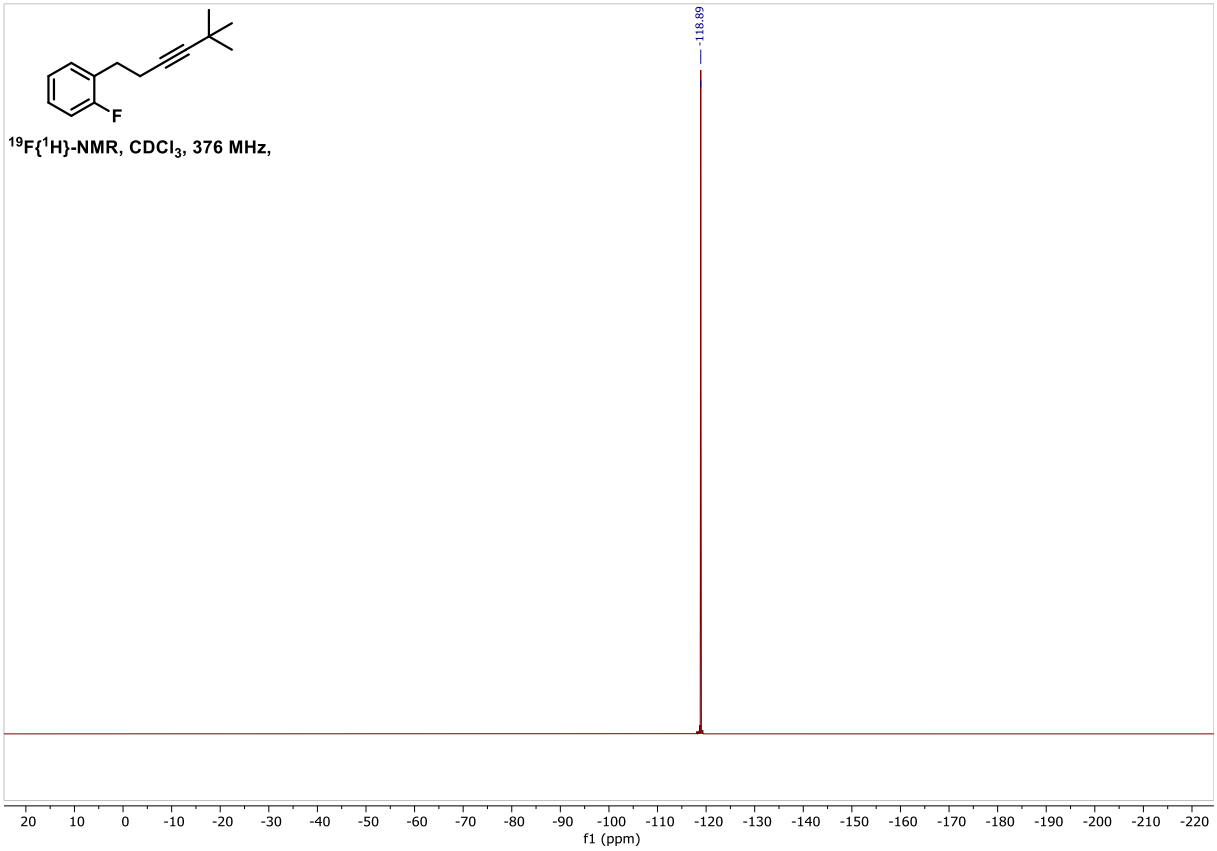
(Z)-1-(5,5-Dimethylhex-3-en-1-yl)-2-methylbenzene (**3.1d**)

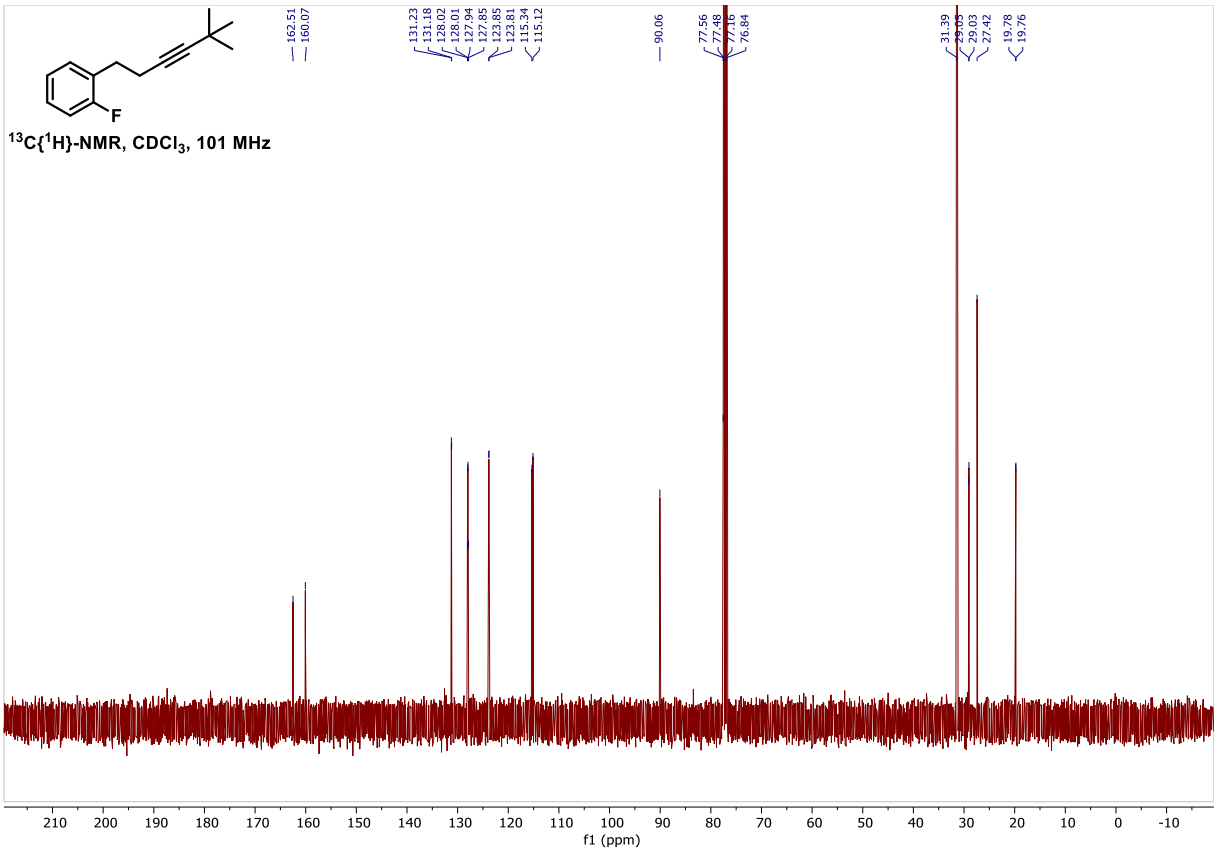




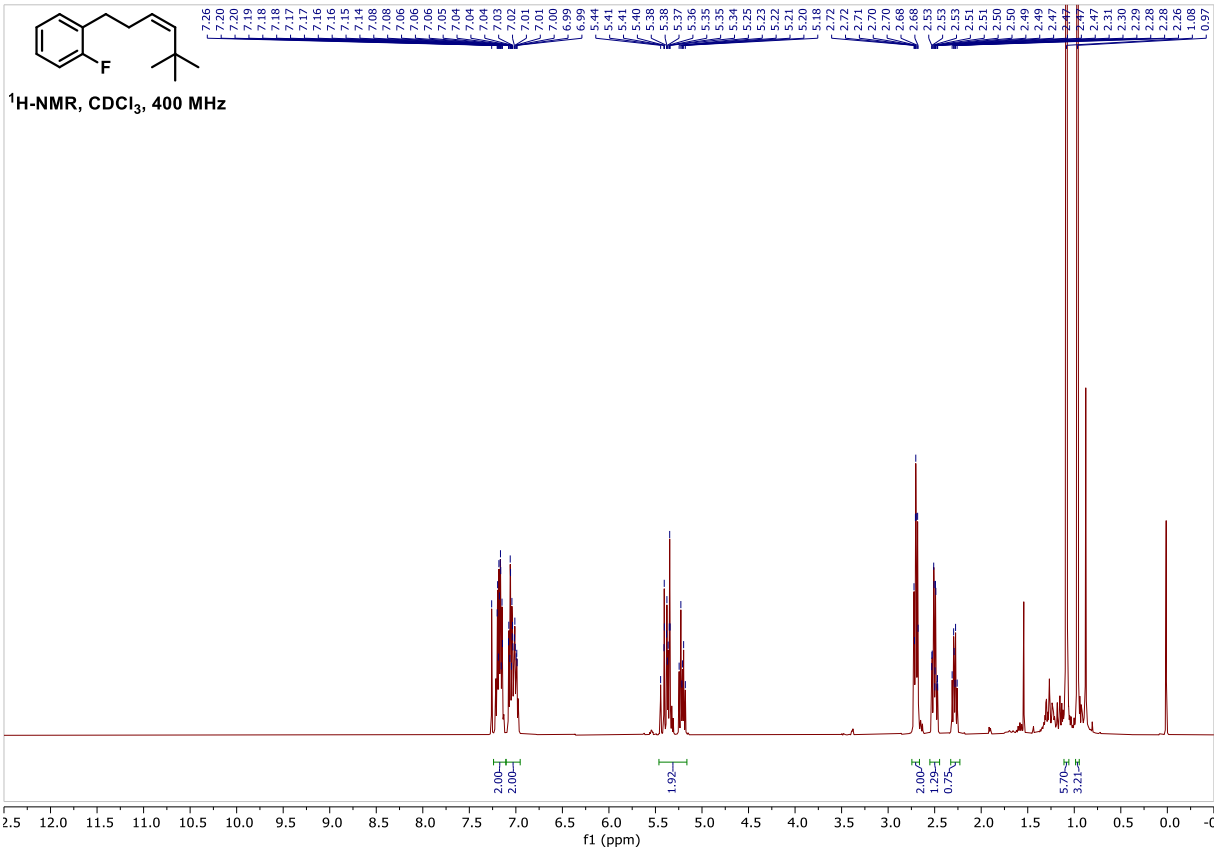
1-(5,5-Dimethylhex-3-yn-1-yl)-2-fluorobenzene (**3.20b**)

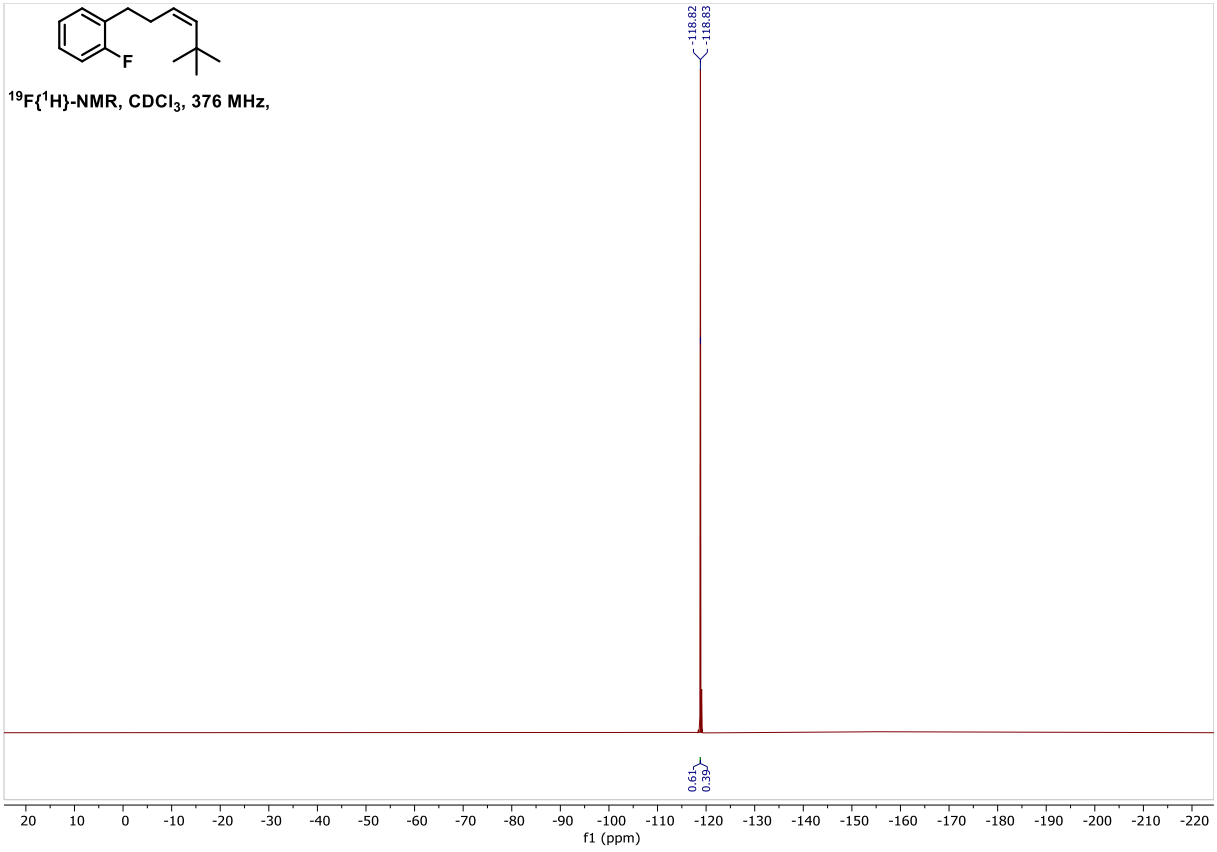


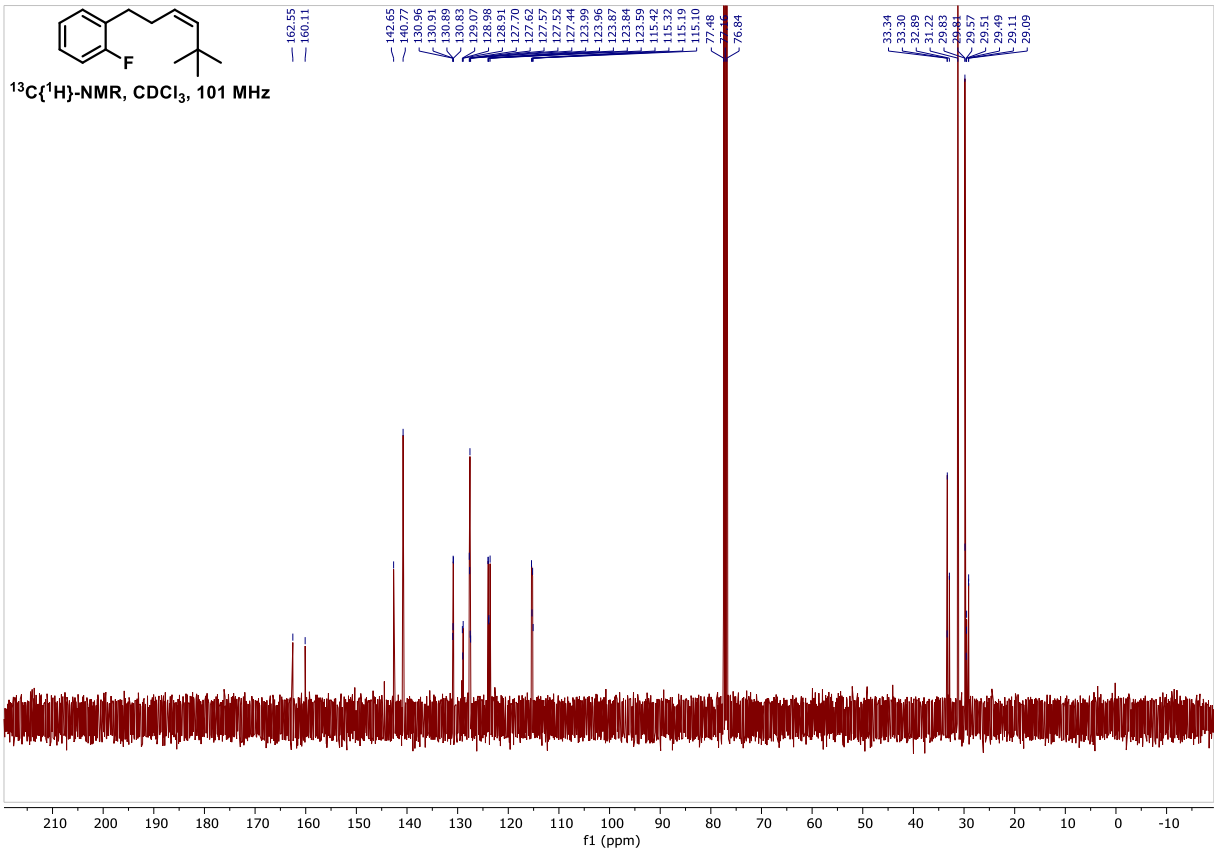




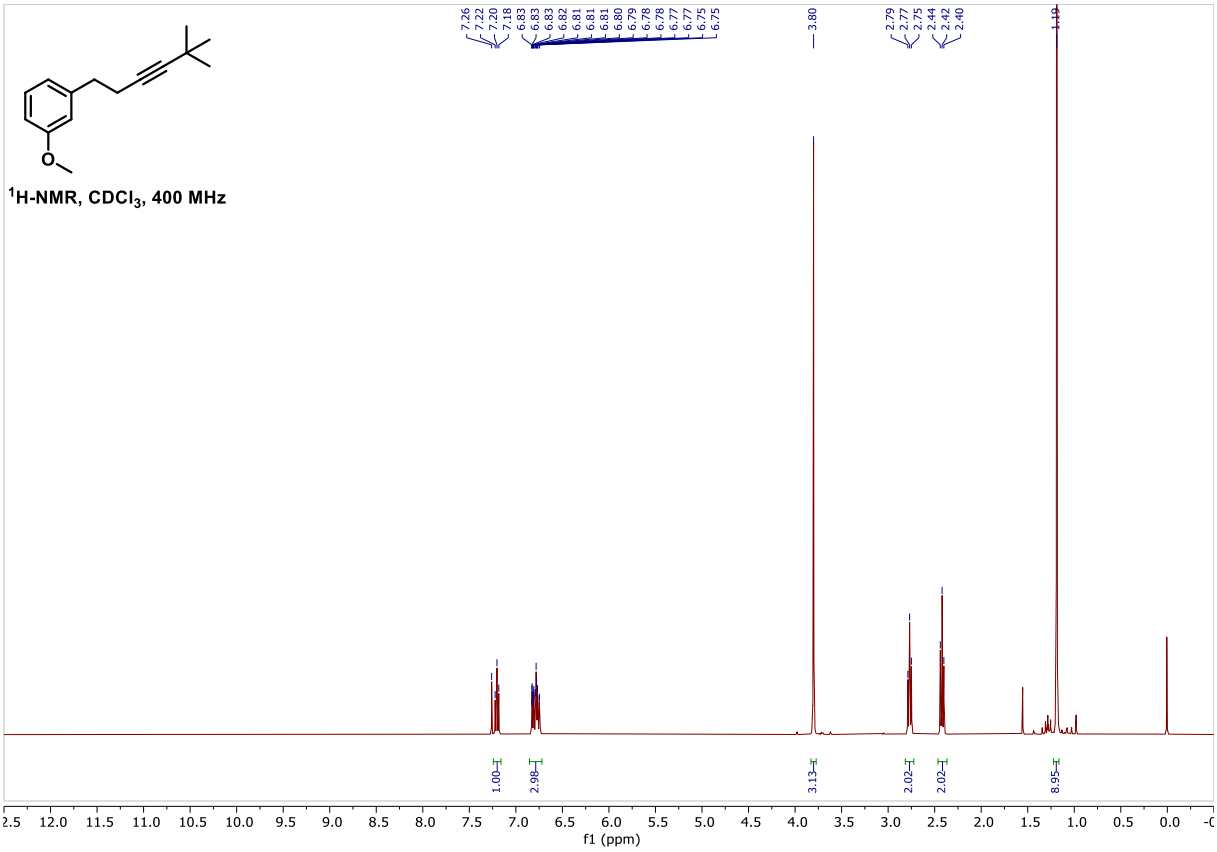
(Z)-1-(5,5-Dimethylhex-3-en-1-yl)-2-fluorobenzene (**3.1e**)

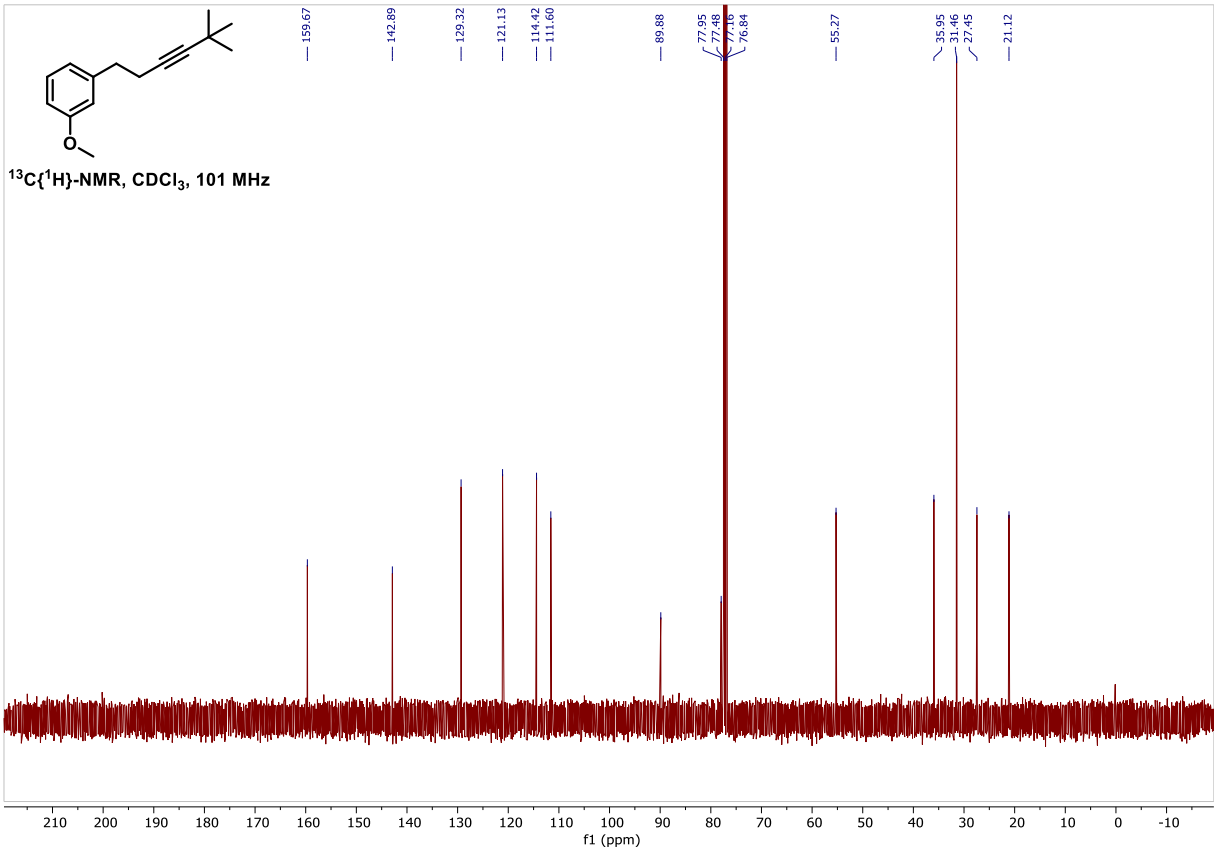



F
$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 376 MHz,
-118.82
-118.83
0.61
0.39
f1 (ppm)

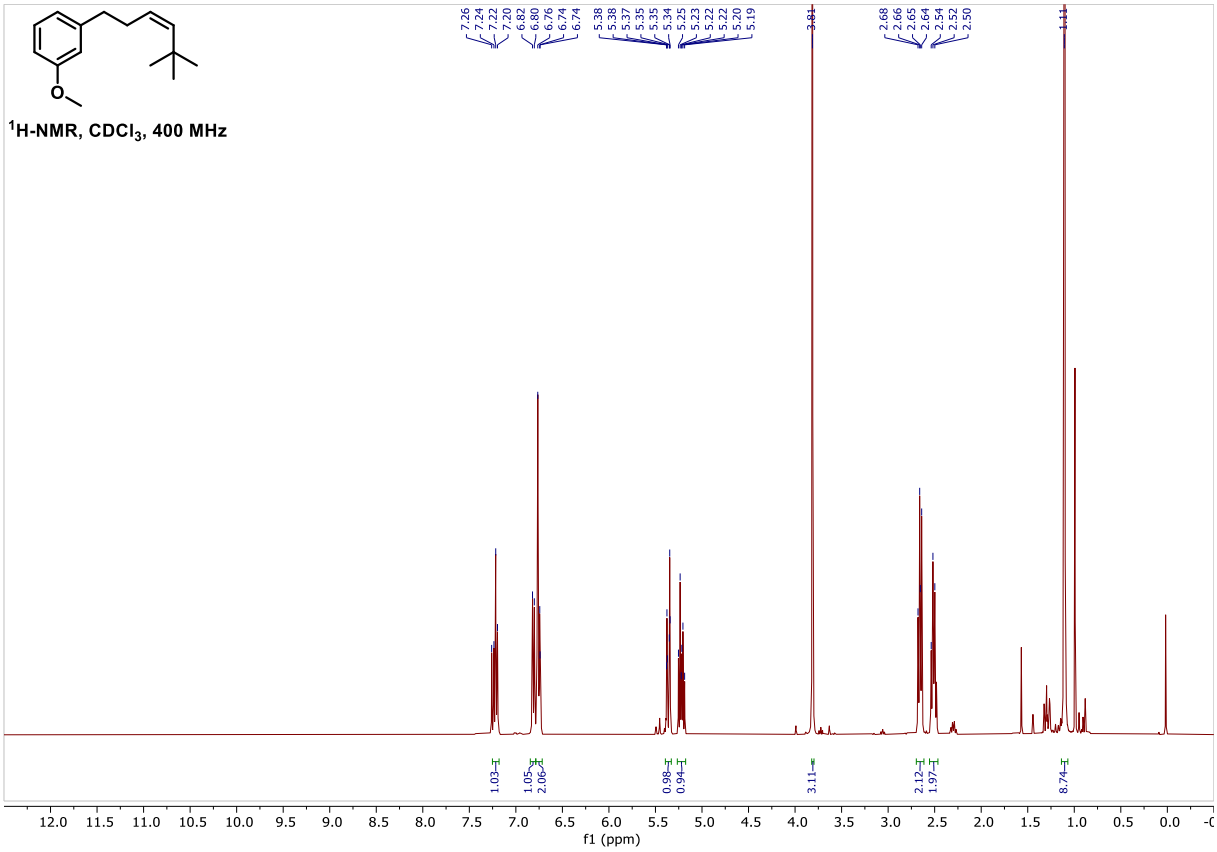

F
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 101 MHz
162.55
160.11
142.65
140.77
130.96
130.91
130.89
130.83
129.07
128.98
128.91
127.70
127.62
127.57
127.52
127.44
123.99
123.96
123.87
123.84
123.59
115.42
115.32
115.19
115.10
77.48
76.84
33.34
33.30
32.89
31.22
29.83
29.81
29.57
29.51
29.49
29.11
29.09
f1 (ppm)

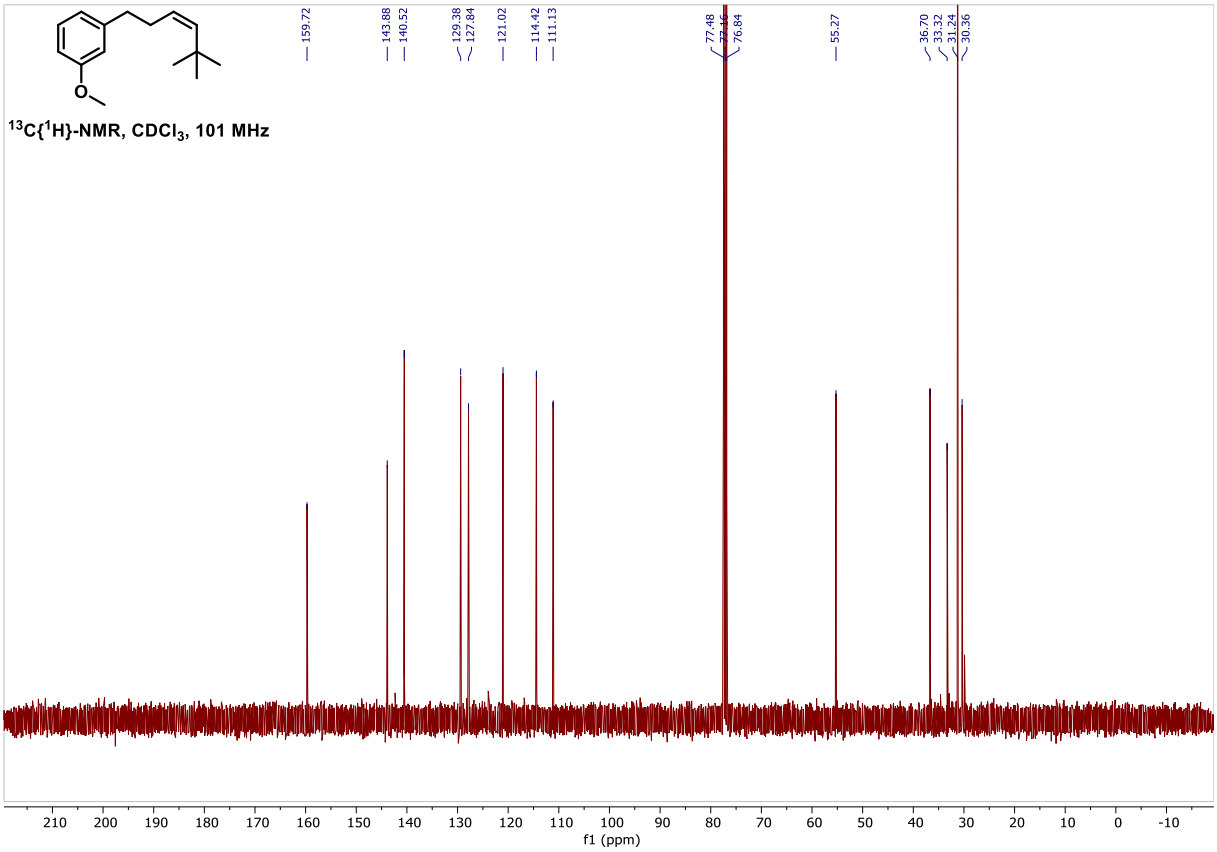
1-(5,5-Dimethylhex-3-yn-1-yl)-3-methoxybenzene (**3.20c**)



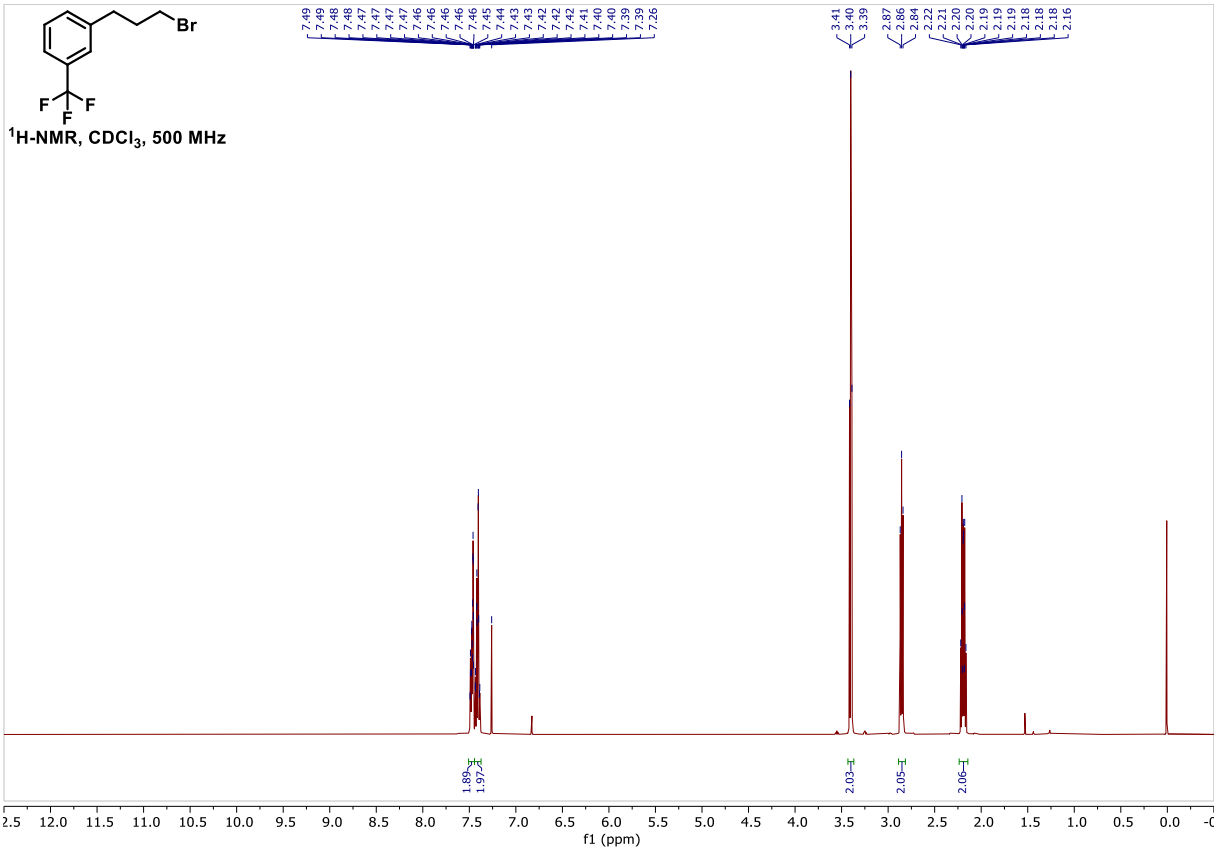


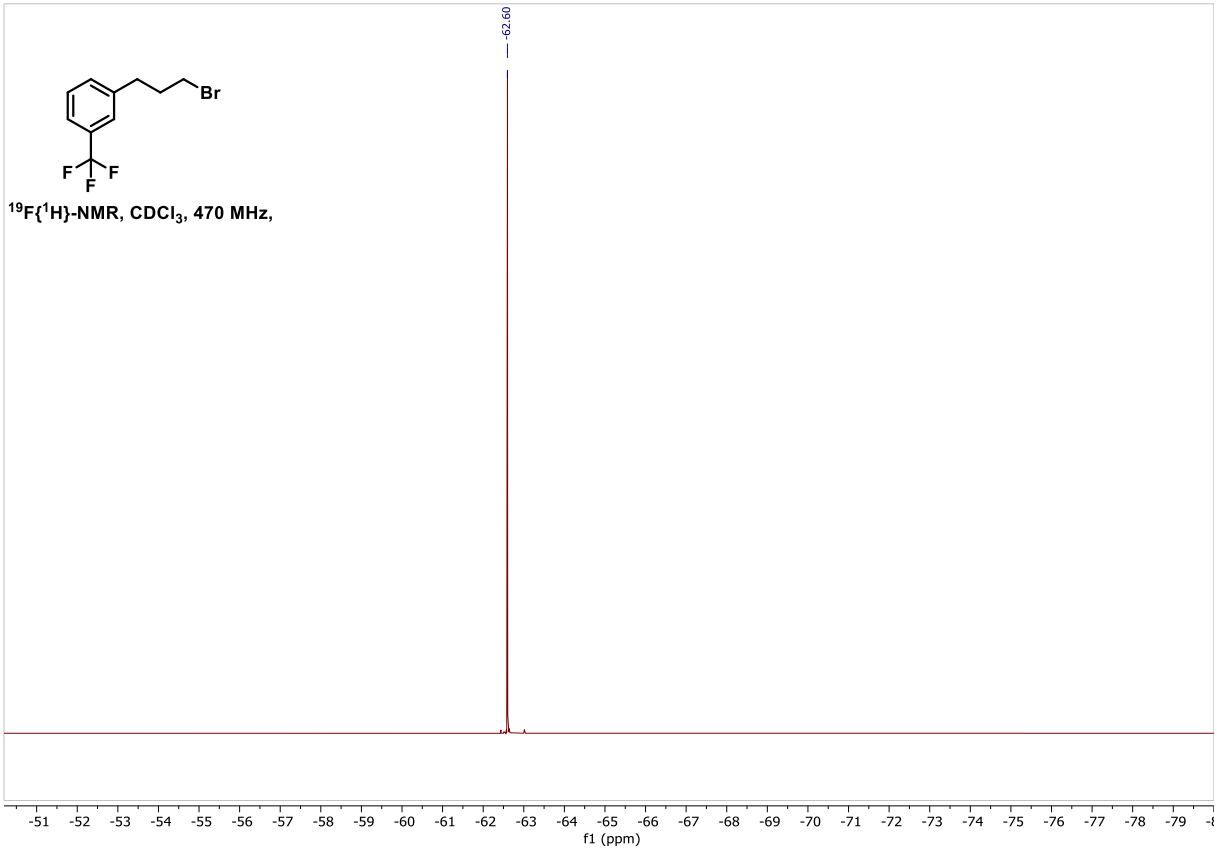
(*Z*)-1-(5,5-Dimethylhex-3-en-1-yl)-3-methoxybenzene (**3.1f**)

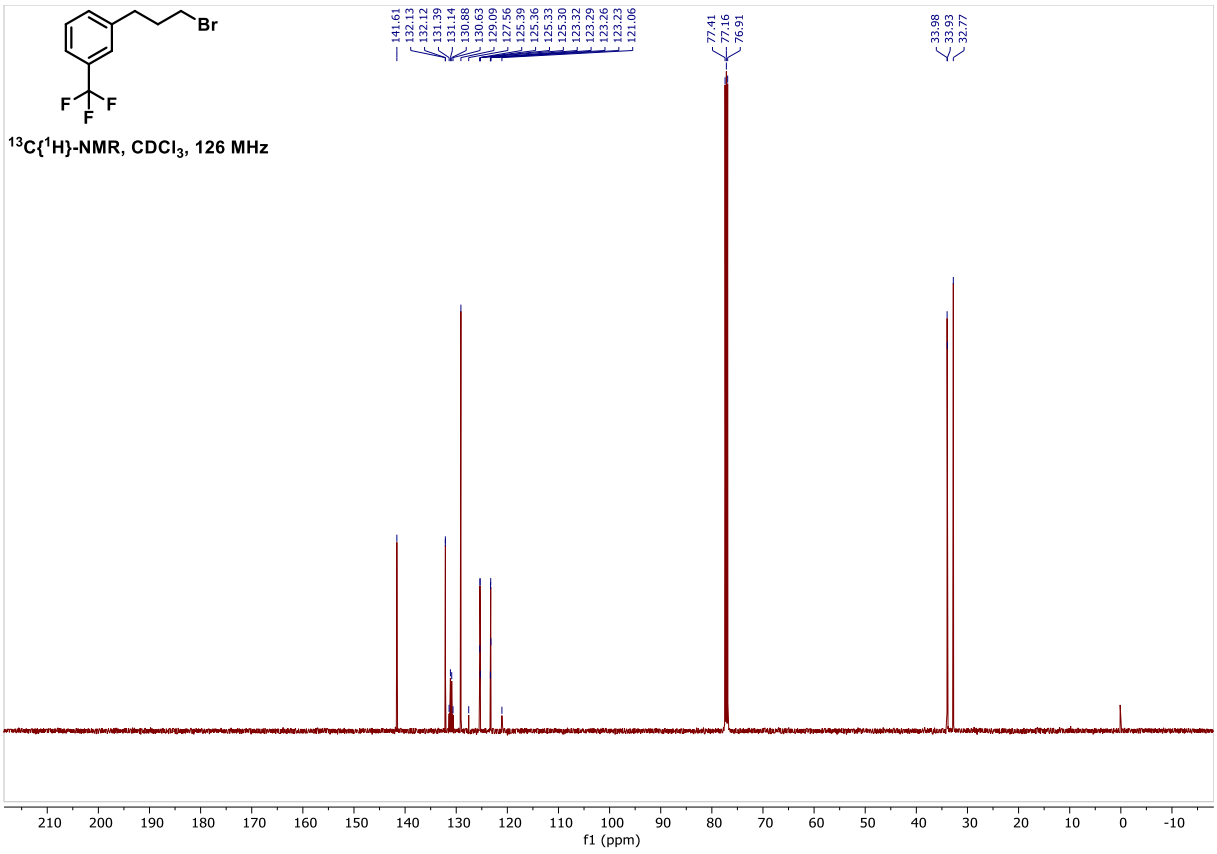




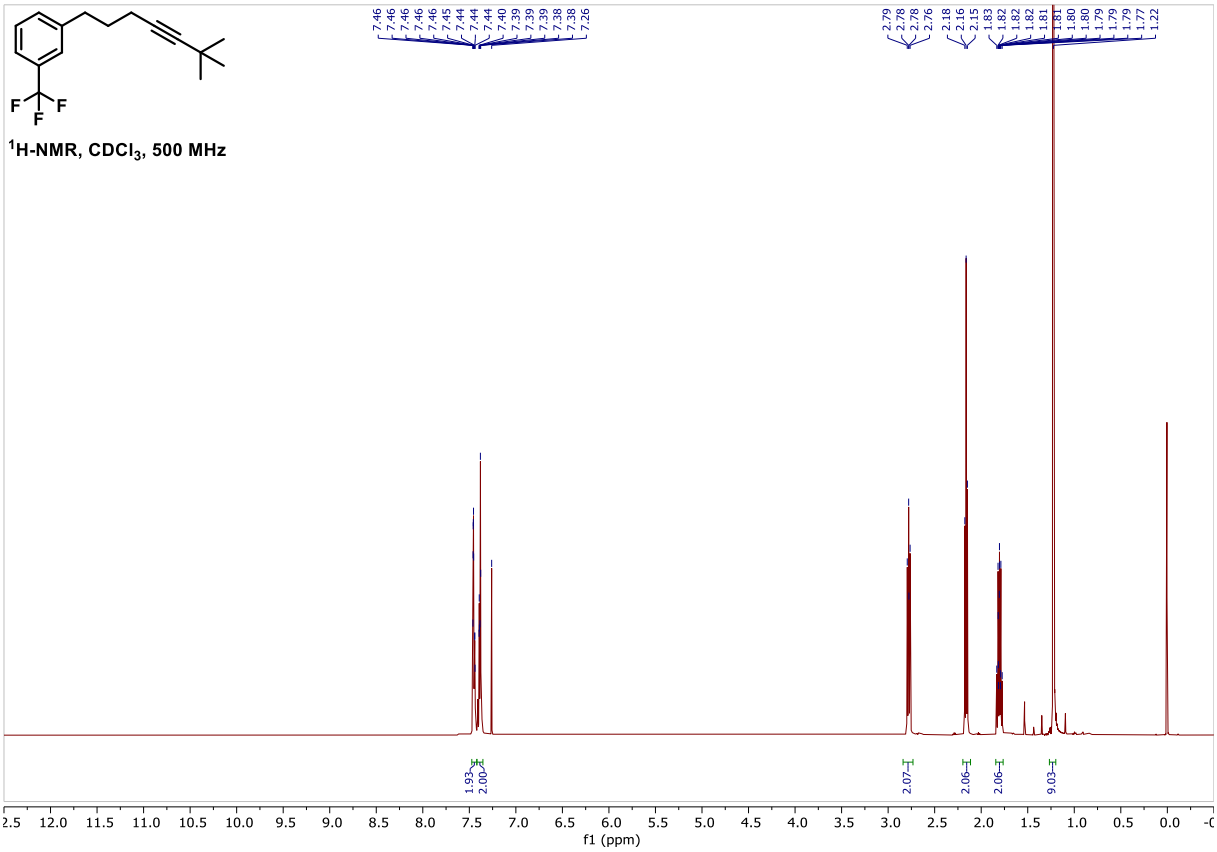
1-(3-Bromopropyl)-3-(trifluoromethyl)benzene (**3.19a**)

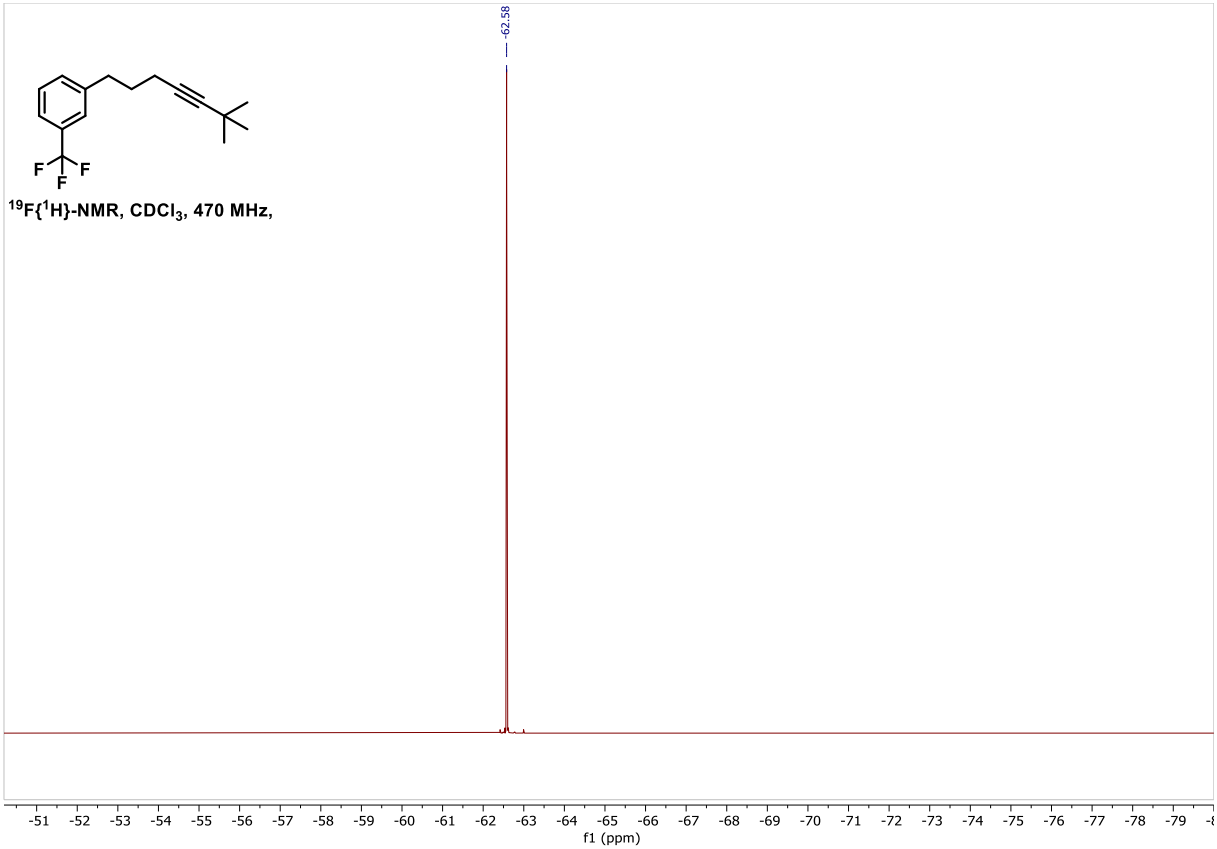




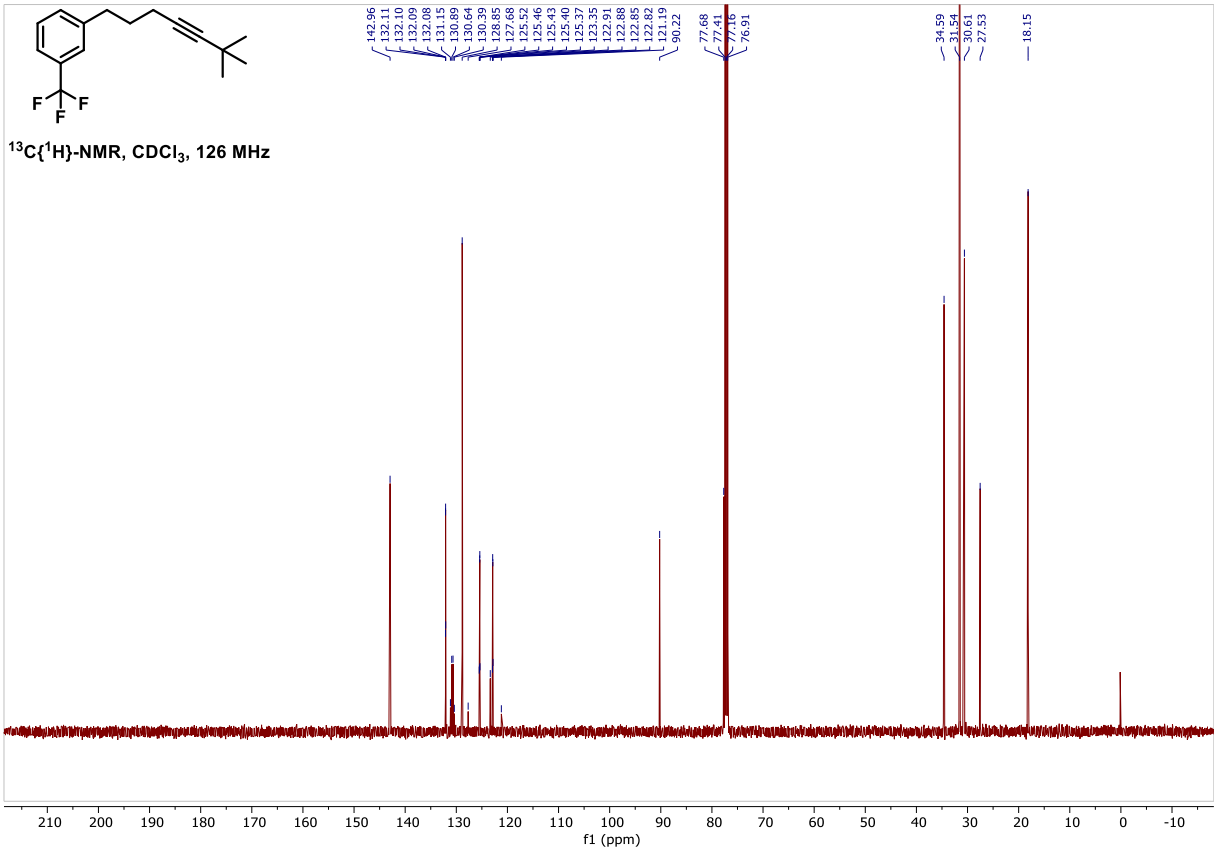


1-(6,6-Dimethylhept-4-yn-1-yl)-3-(trifluoromethyl)benzene (**3.20d**)



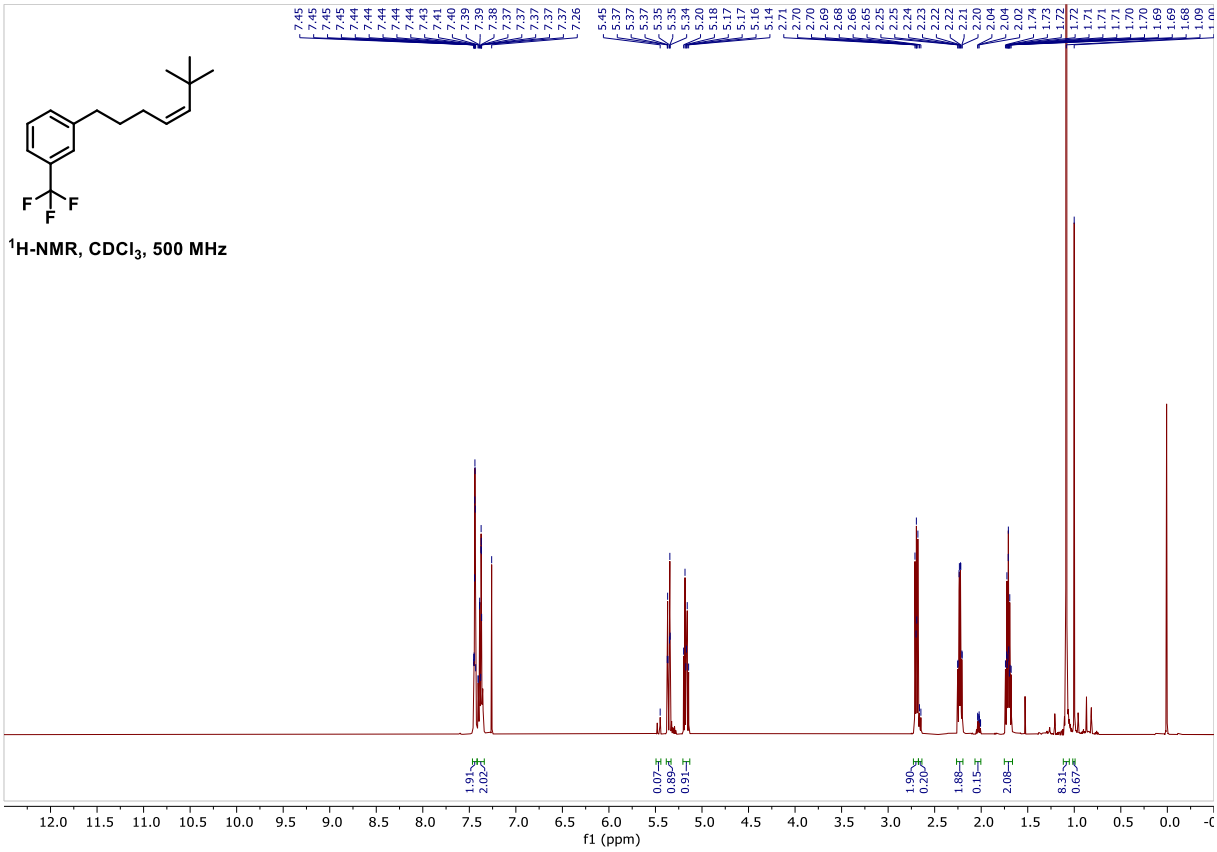


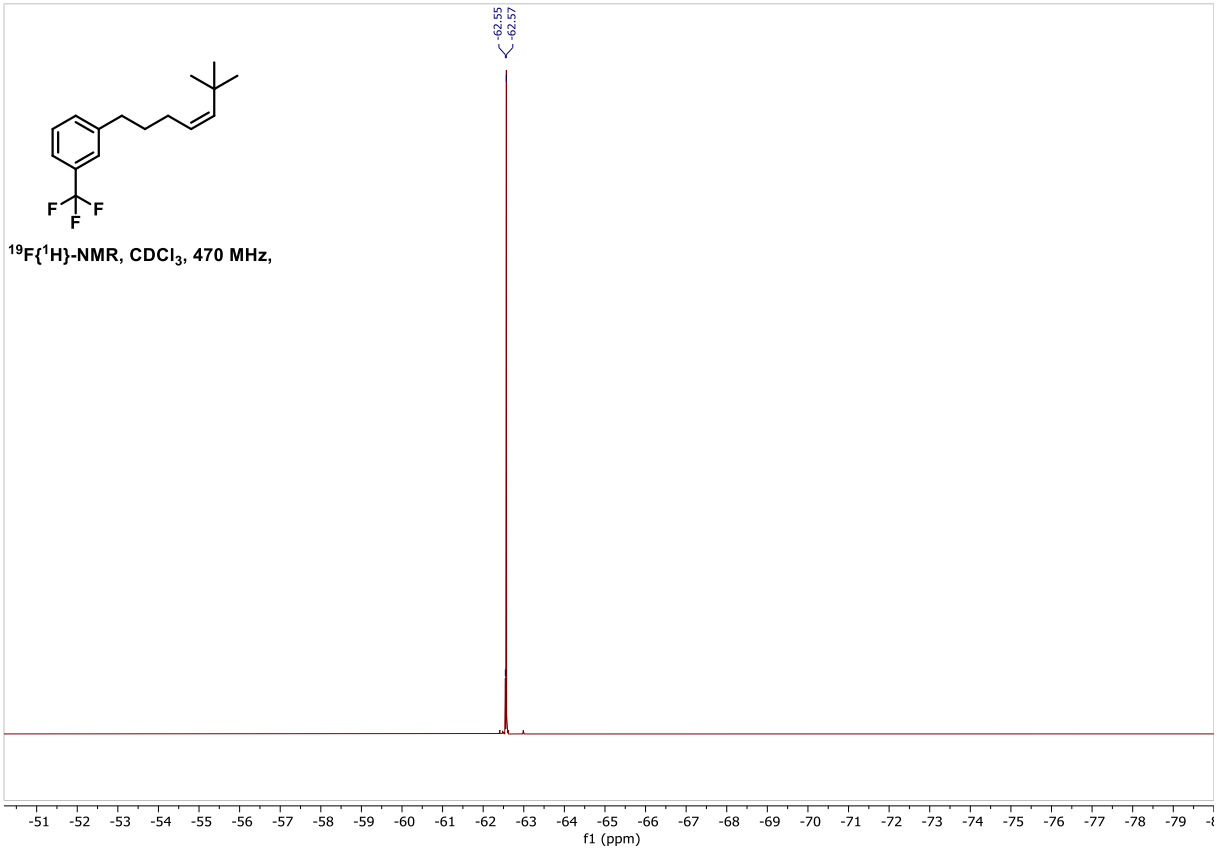
$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 470 MHz,

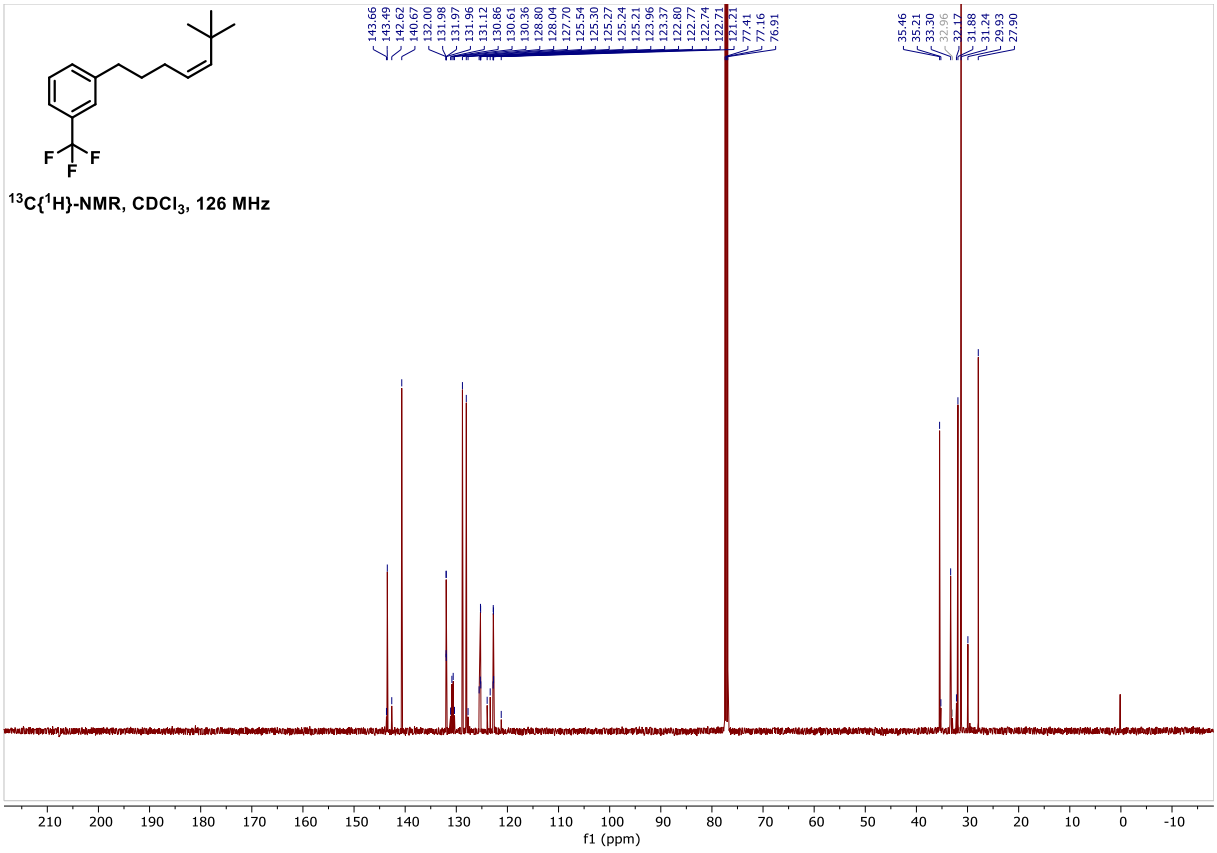


$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz

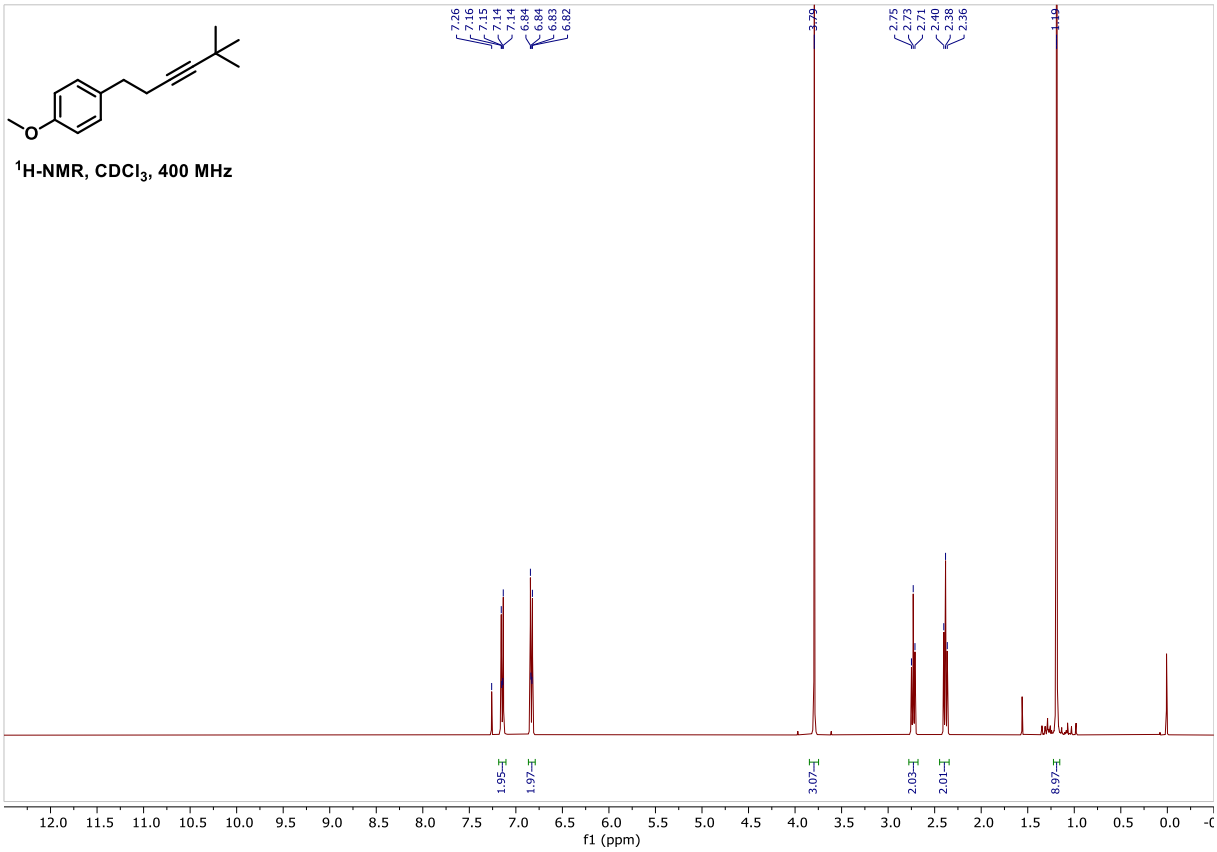
(*Z*)-1-(6,6-Dimethylhept-4-en-1-yl)-3-(trifluoromethyl)benzene (**3.1g**)

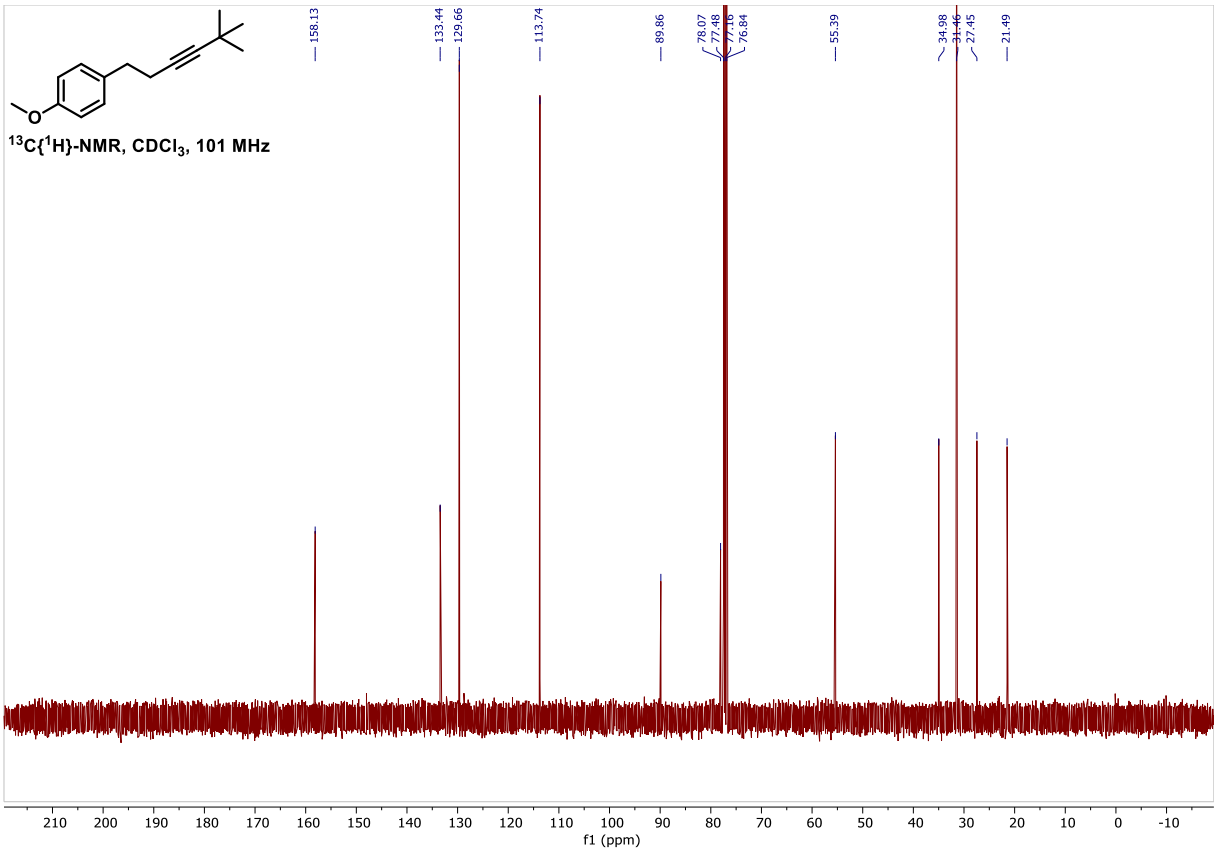




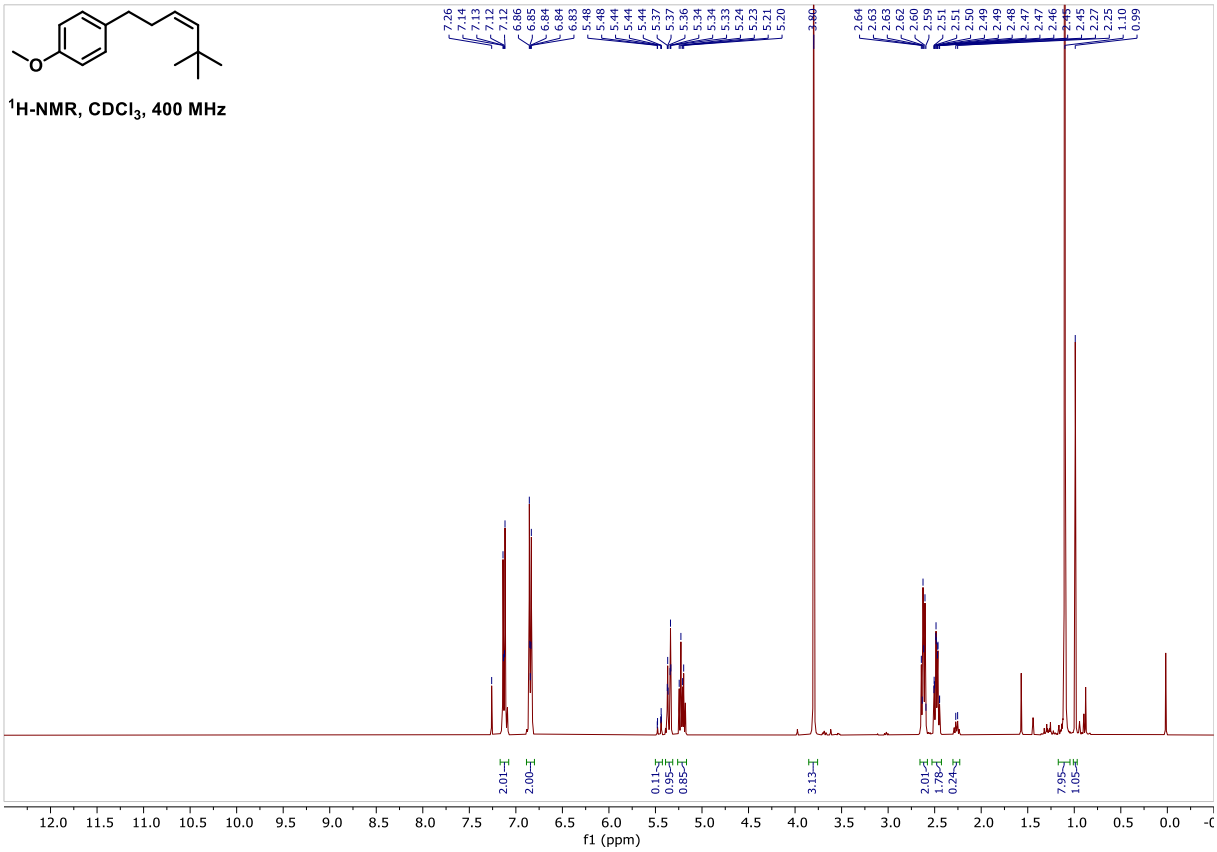


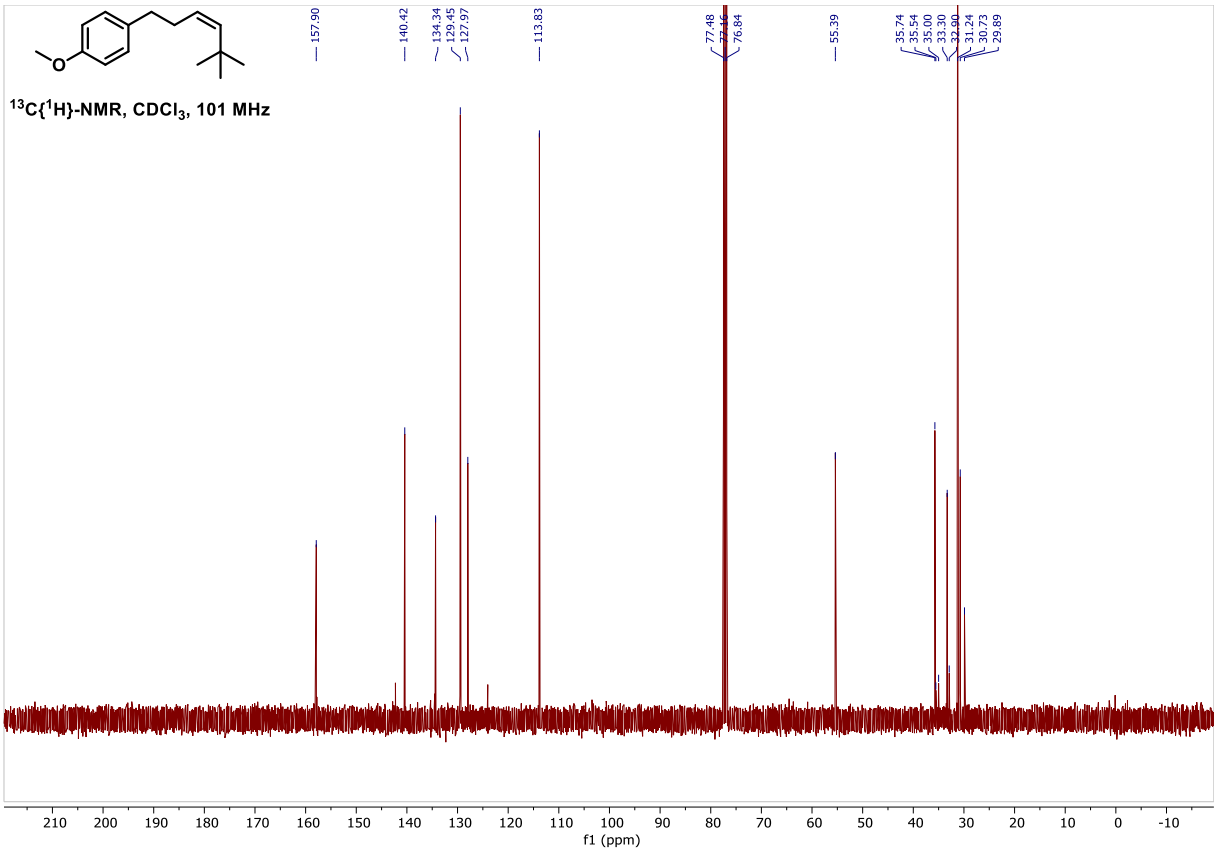
1-(5,5-Dimethylhex-3-yn-1-yl)-4-methoxybenzene (**3.20e**)



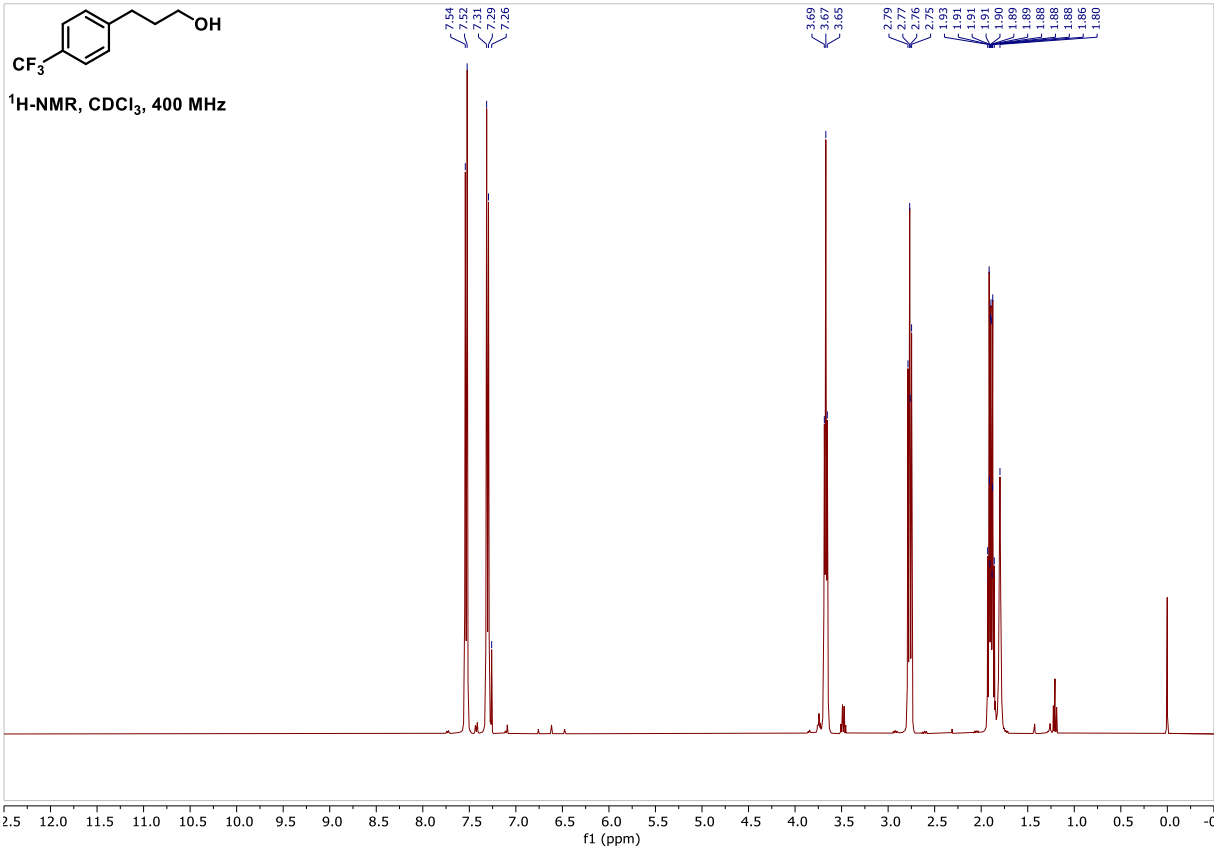


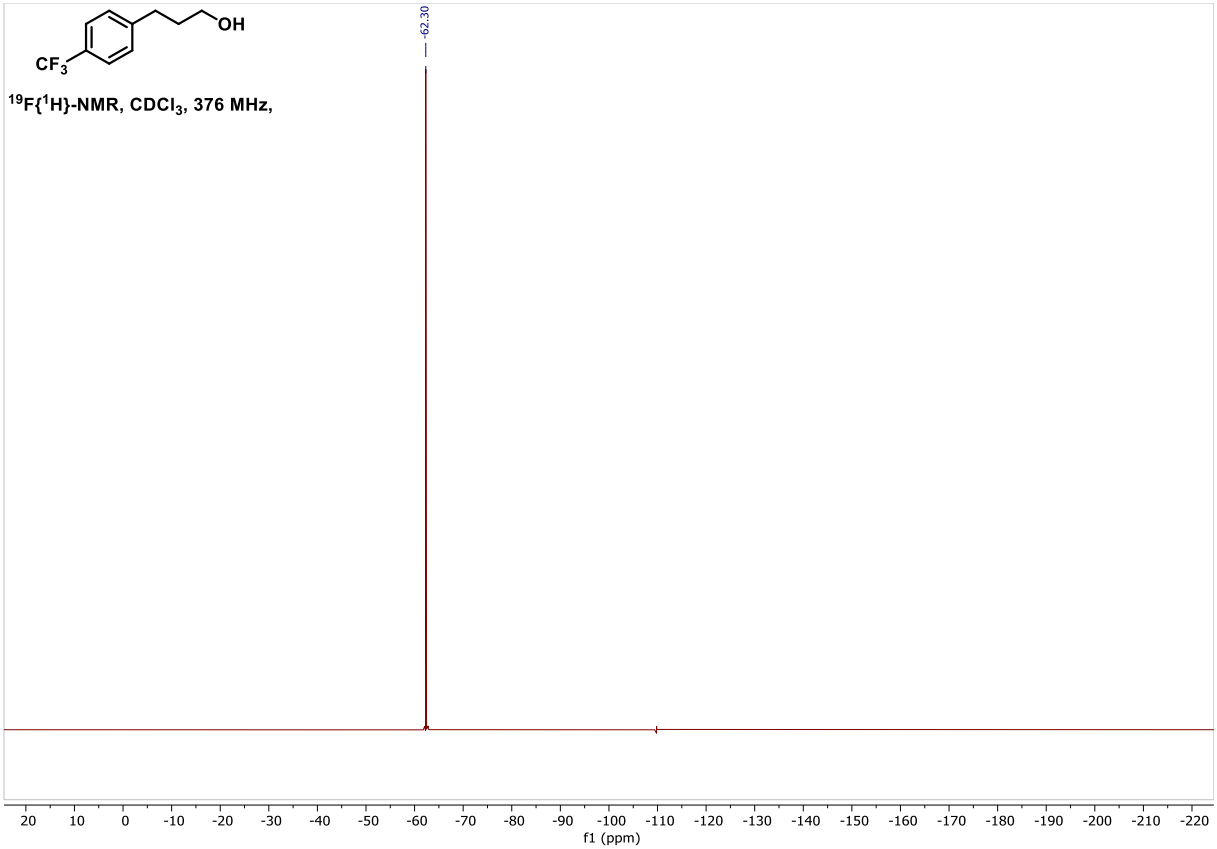
(*Z*)-1-(5,5-Dimethylhex-3-en-1-yl)-4-methoxybenzene (**3.1h**)

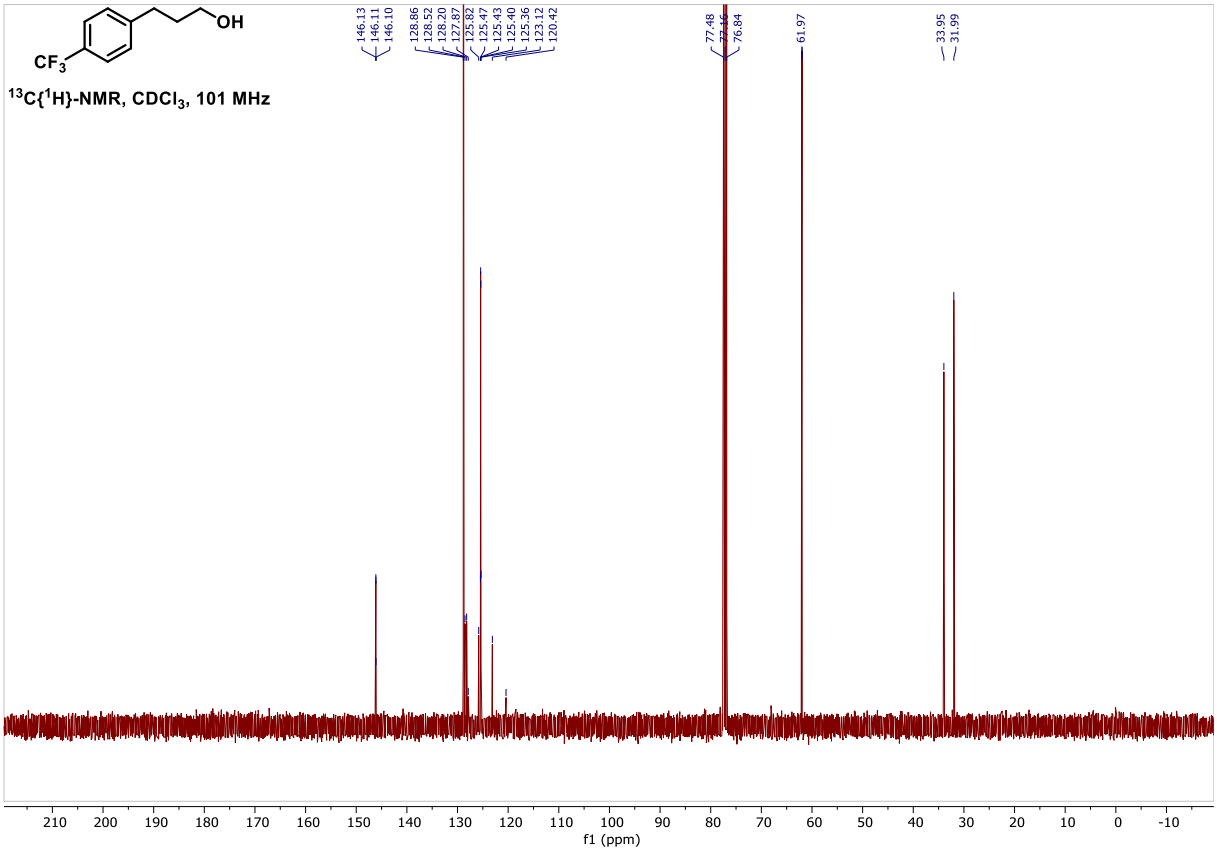




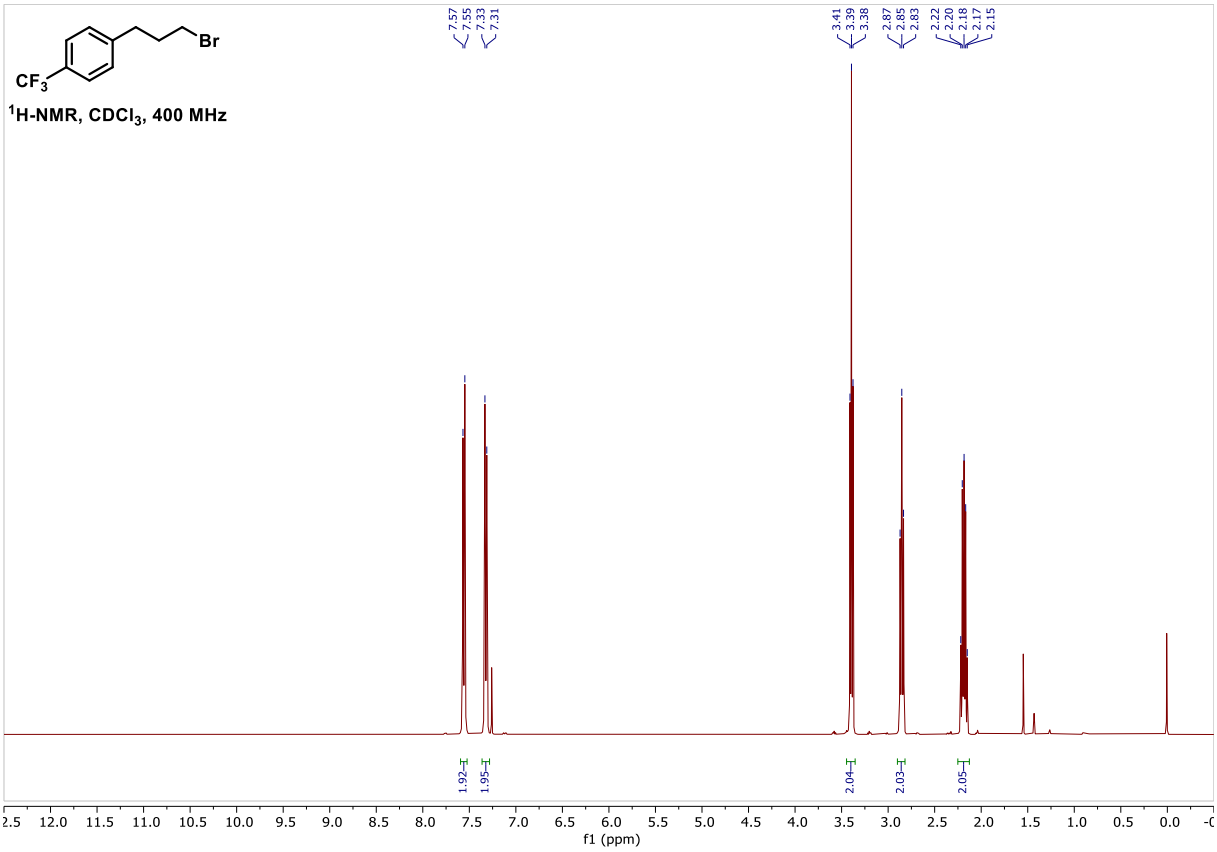
3-(4-(Trifluoromethyl)phenyl)propan-1-ol (**3.14b**)

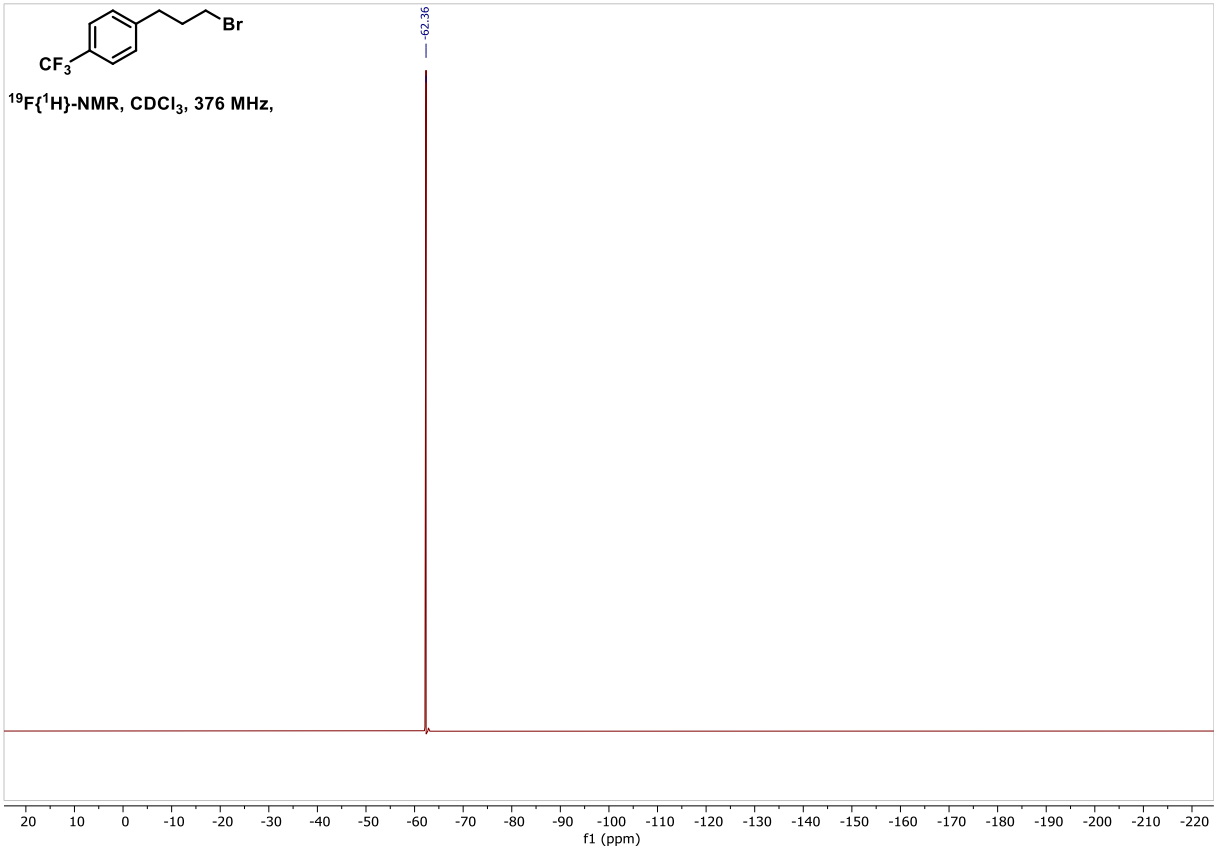


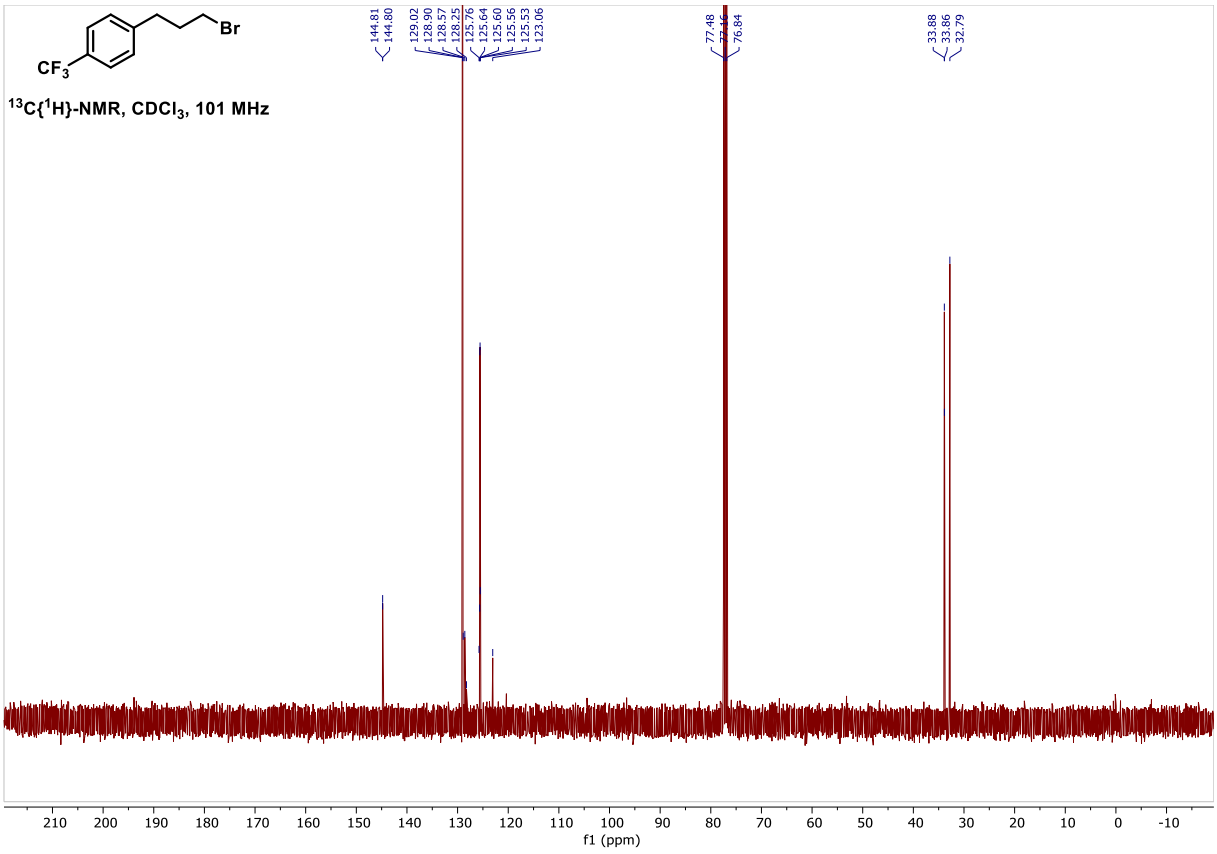

OH
CF3
19F{1H}-NMR, CDCl3, 376 MHz,
-62.30
f1 (ppm)


OH
CF3
13C{1H}-NMR, CDCl3, 101 MHz
146.13
146.11
146.10
128.86
128.52
128.20
127.87
125.82
125.47
125.43
125.40
125.36
123.12
120.42
77.48
77.16
76.84
61.97
33.95
31.99
f1 (ppm)

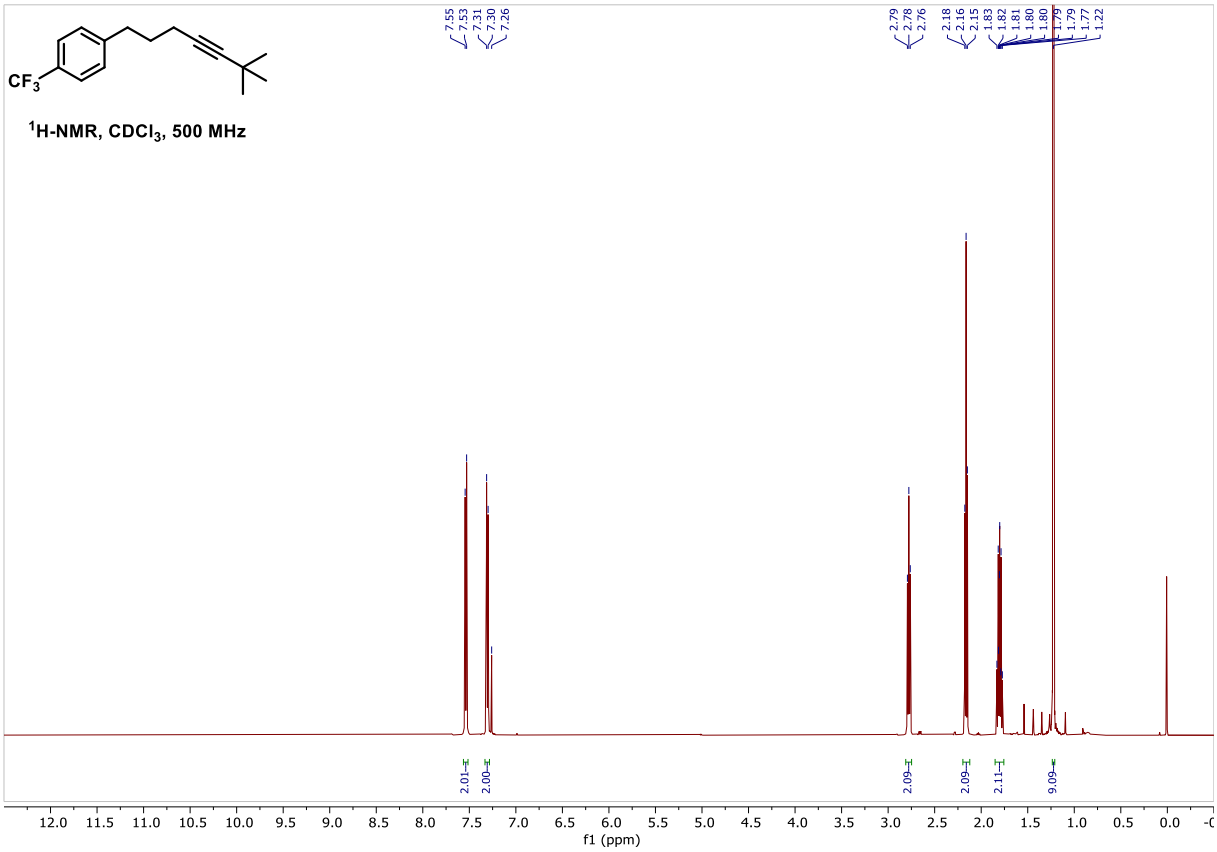
1-(3-Bromopropyl)-4-(trifluoromethyl)benzene (**3.19b**)

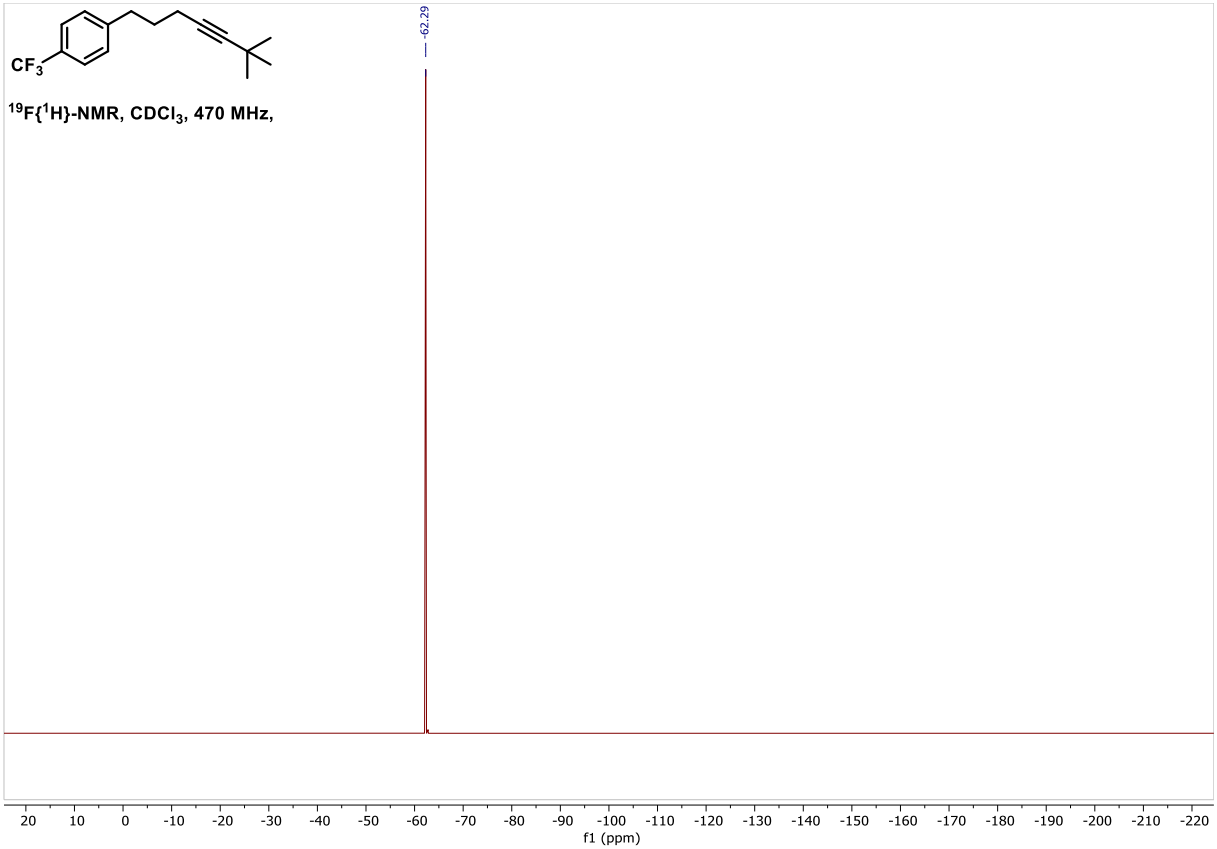




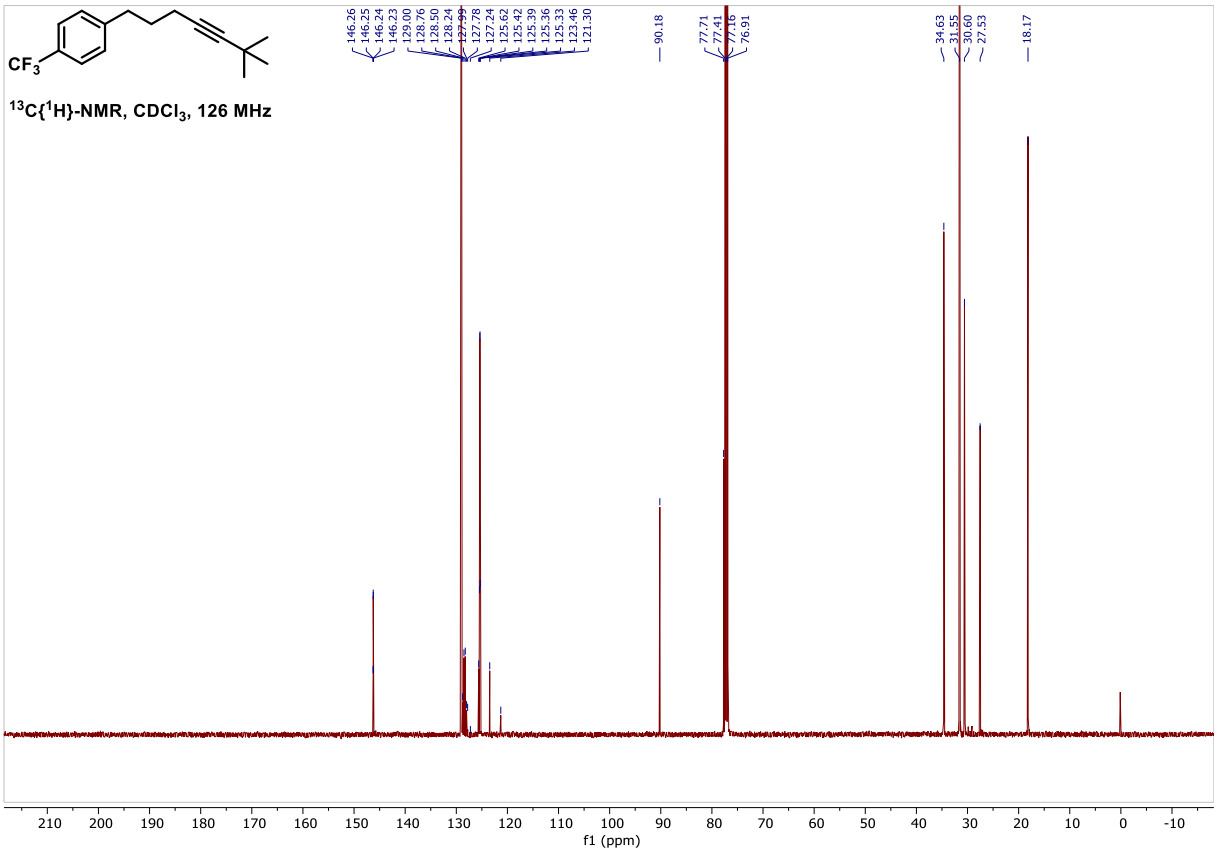


1-(6,6-Dimethylhept-4-yn-1-yl)-4-(trifluoromethyl)benzene (**3.20f**)



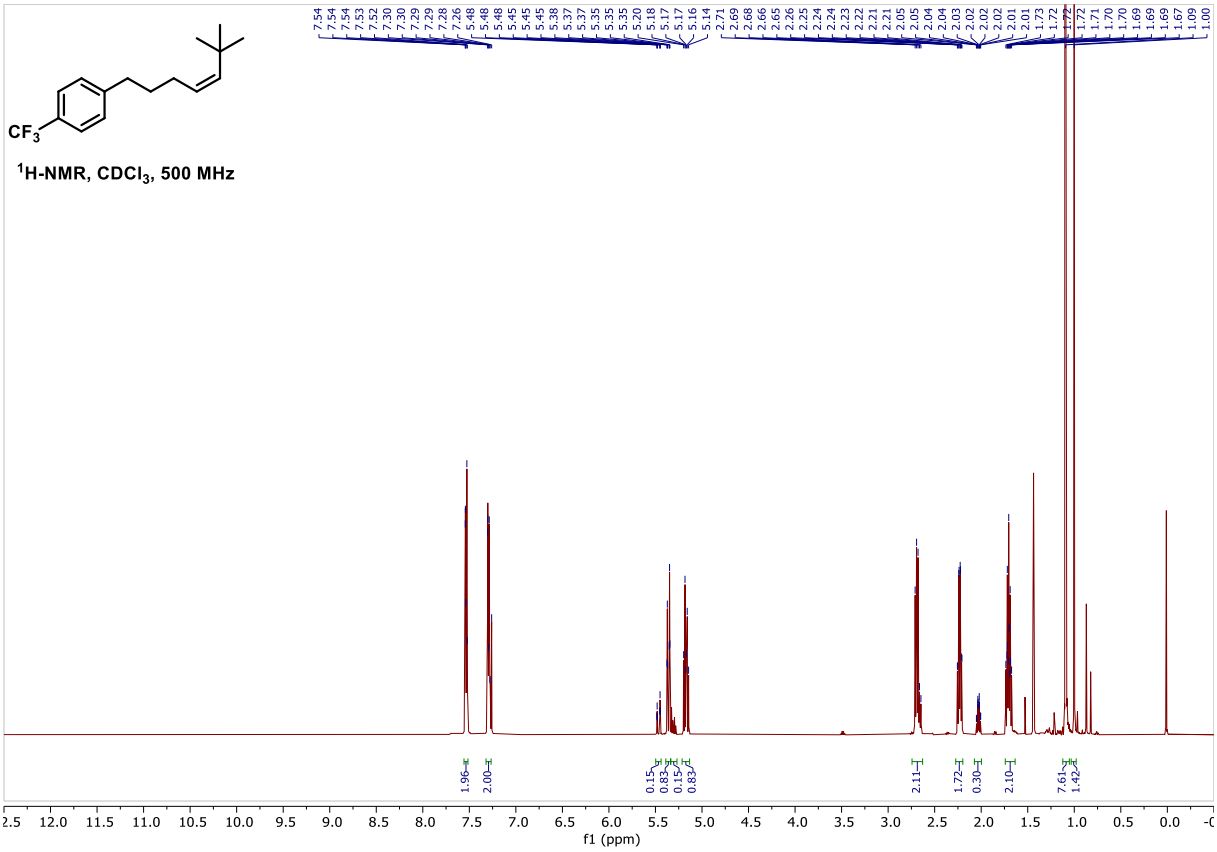


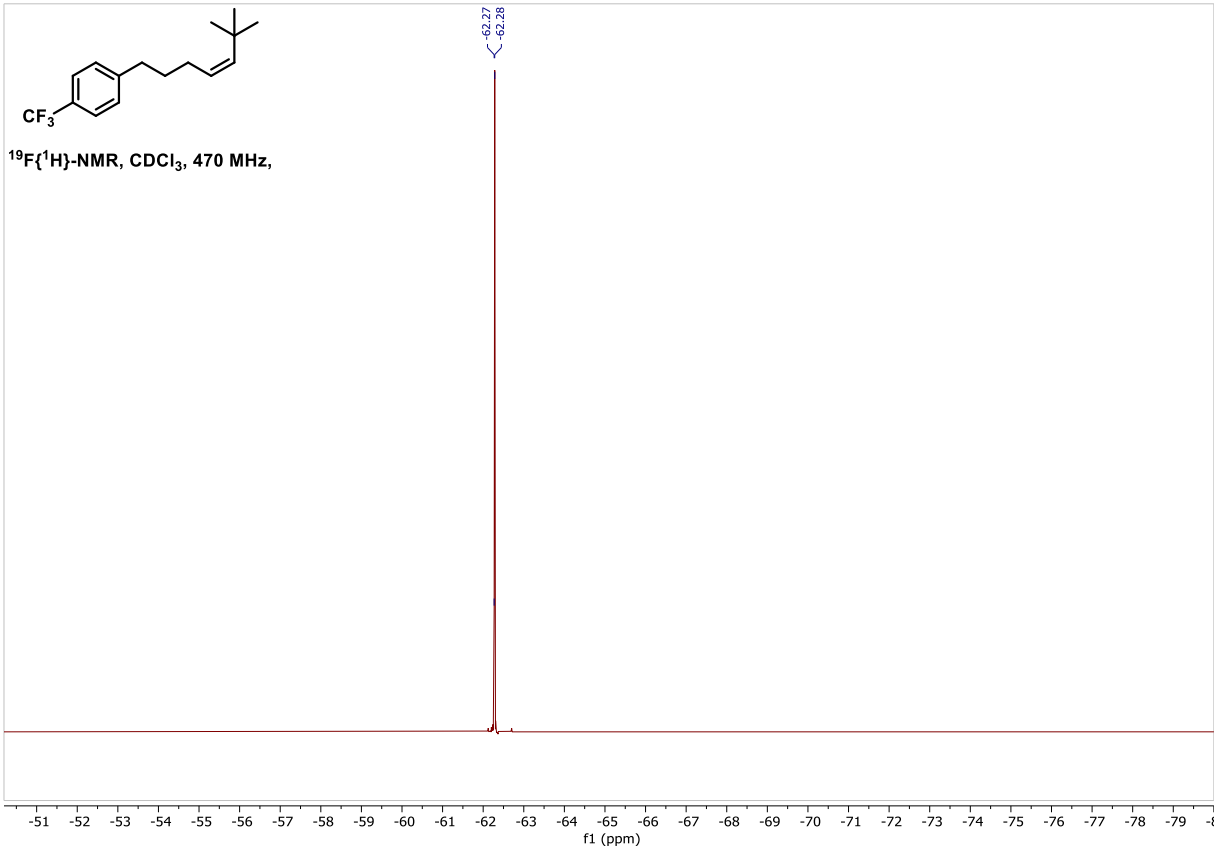
$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 470 MHz,

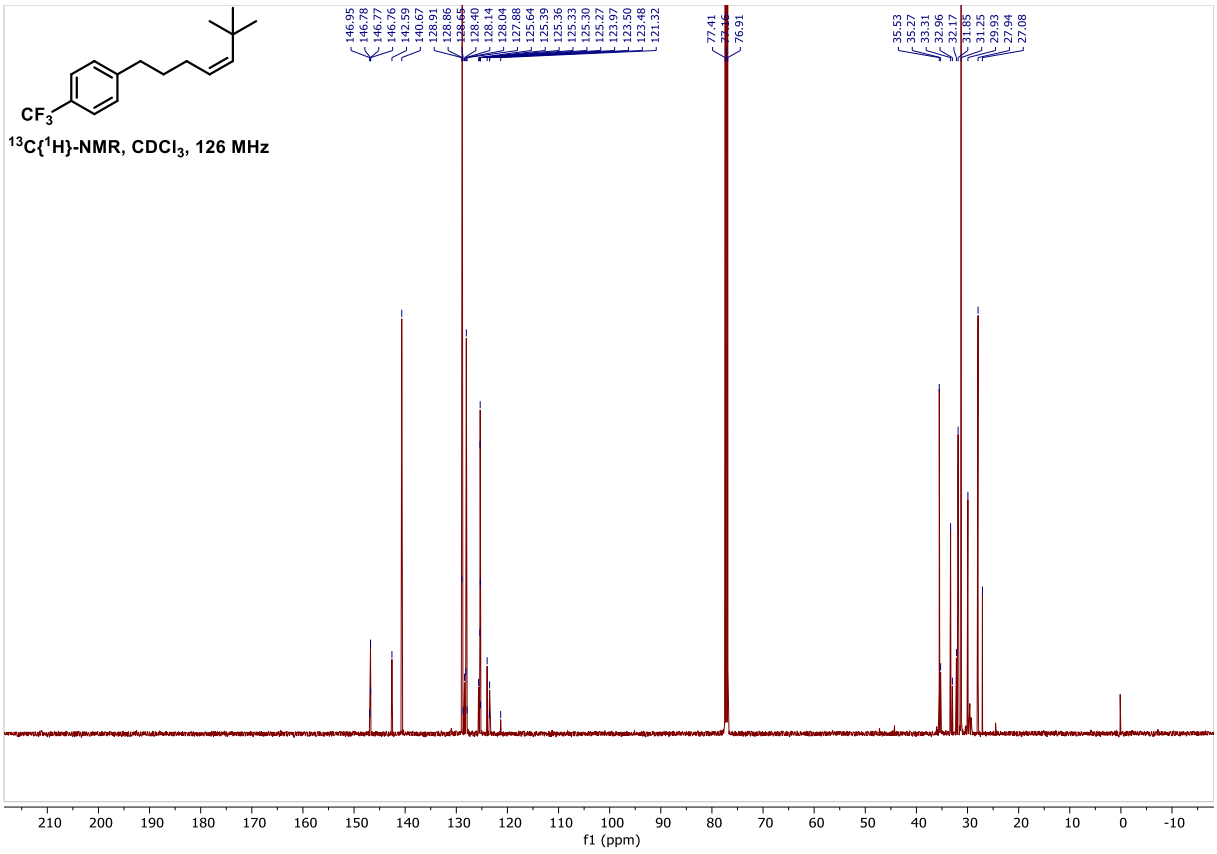


$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz

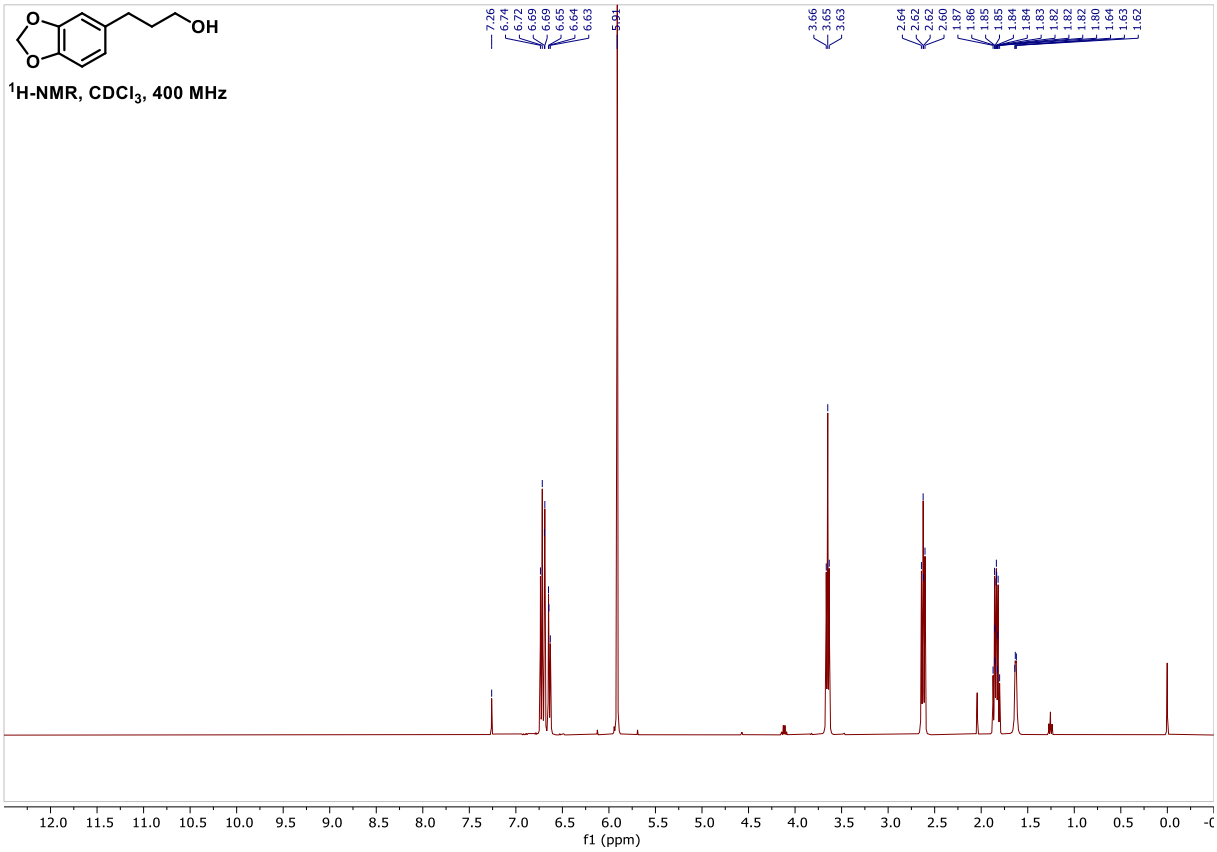
(*Z*)-1-(6,6-Dimethylhept-4-en-1-yl)-4-(trifluoromethyl)benzene (**3.1i**)

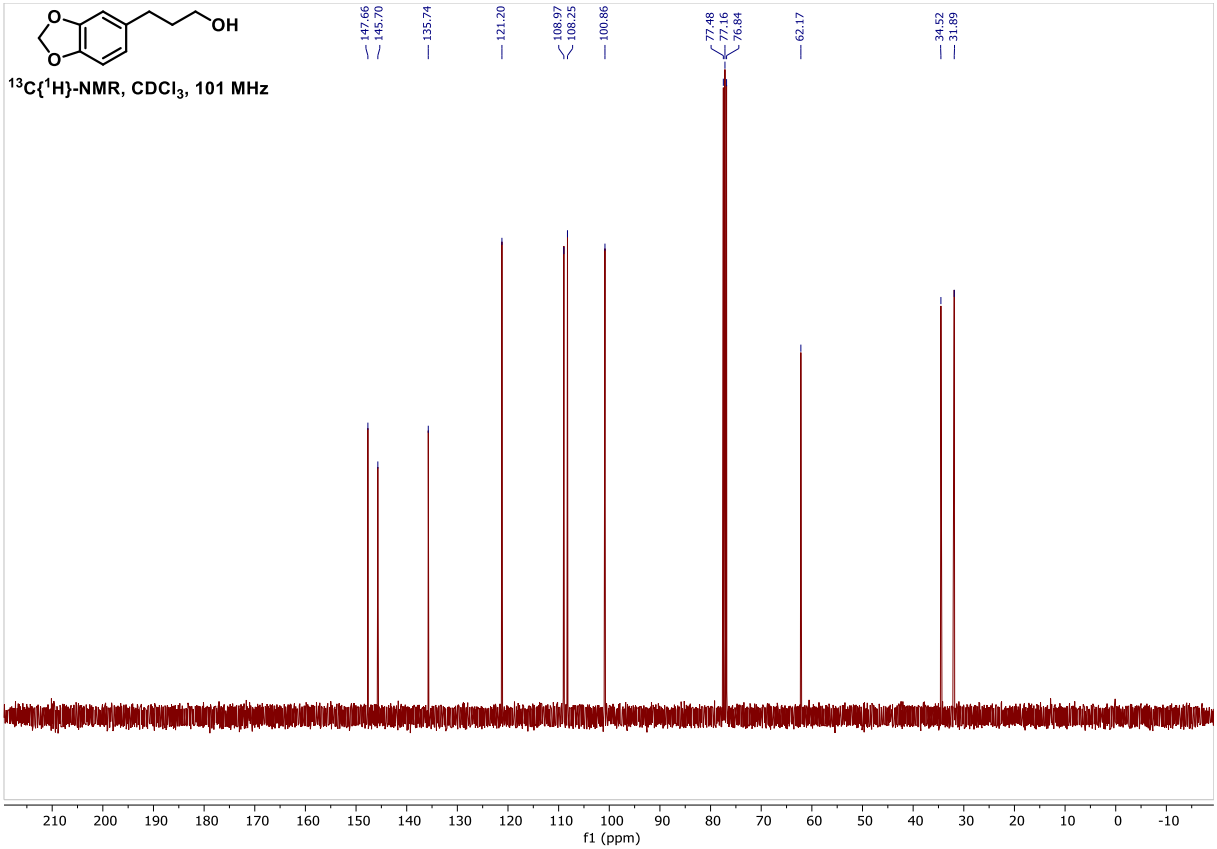




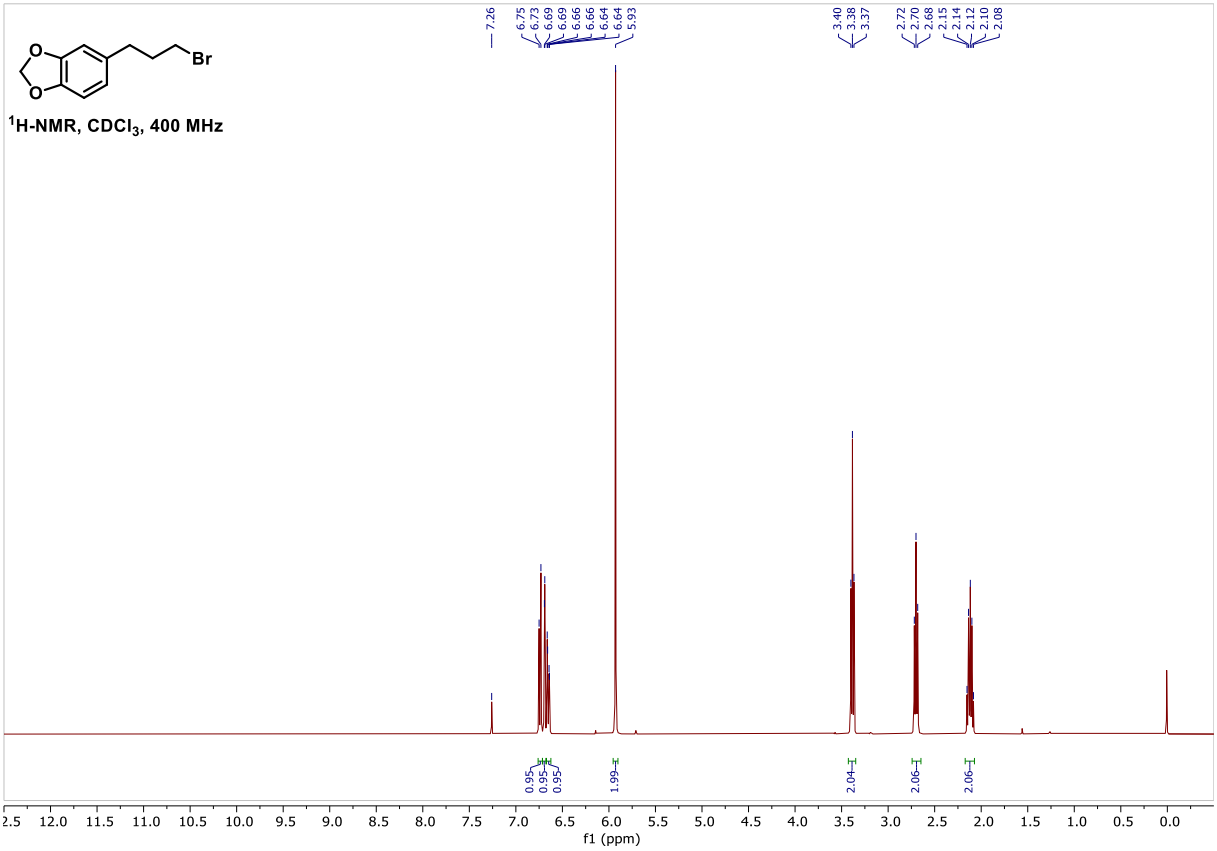


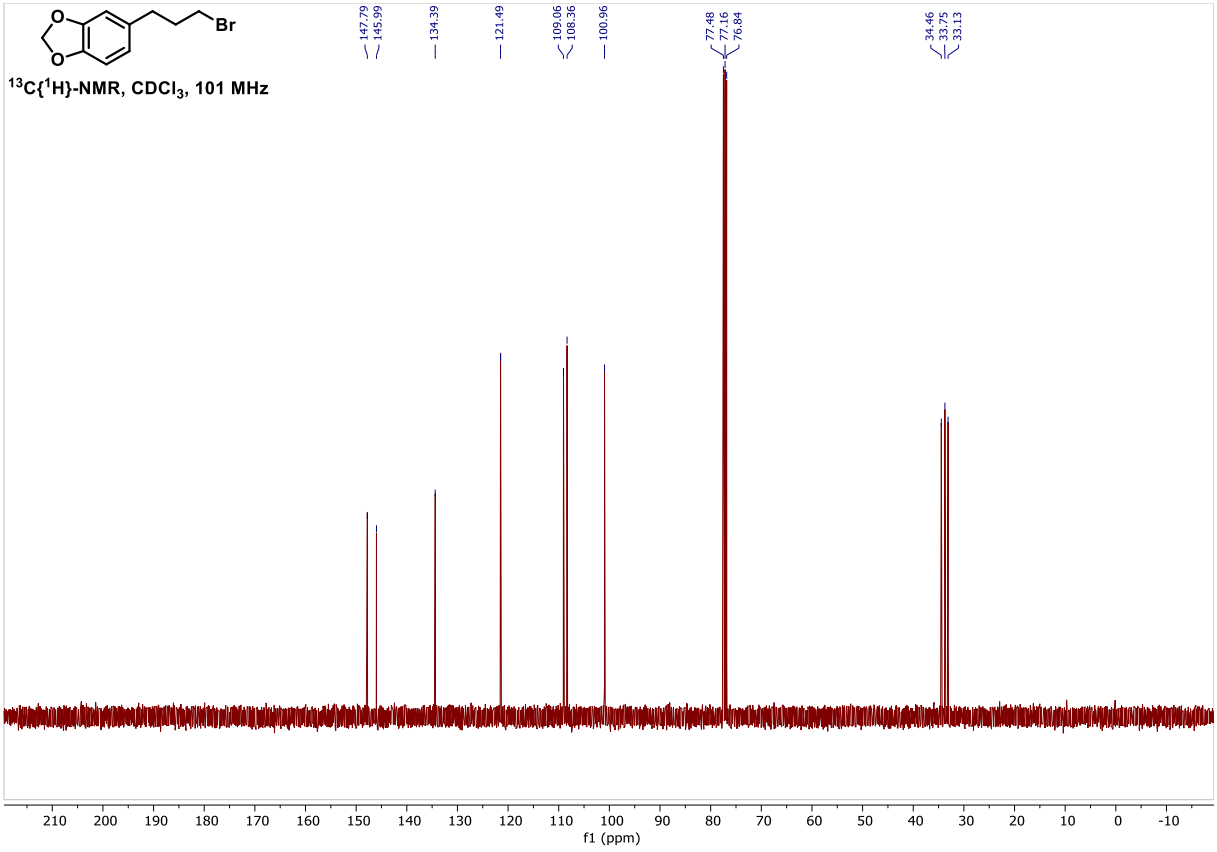
3-(Benzo-dioxol-5-yl)propan-1-ol (**3.14c**)



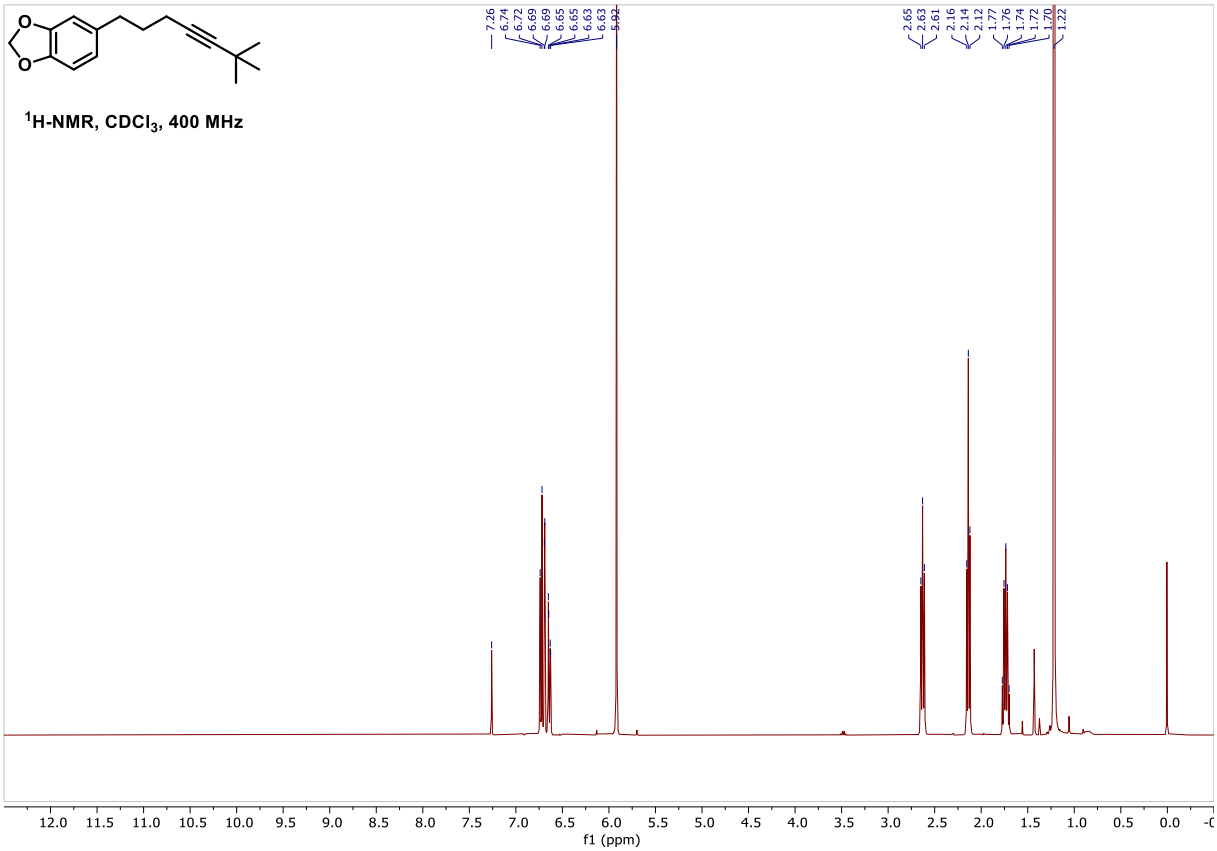


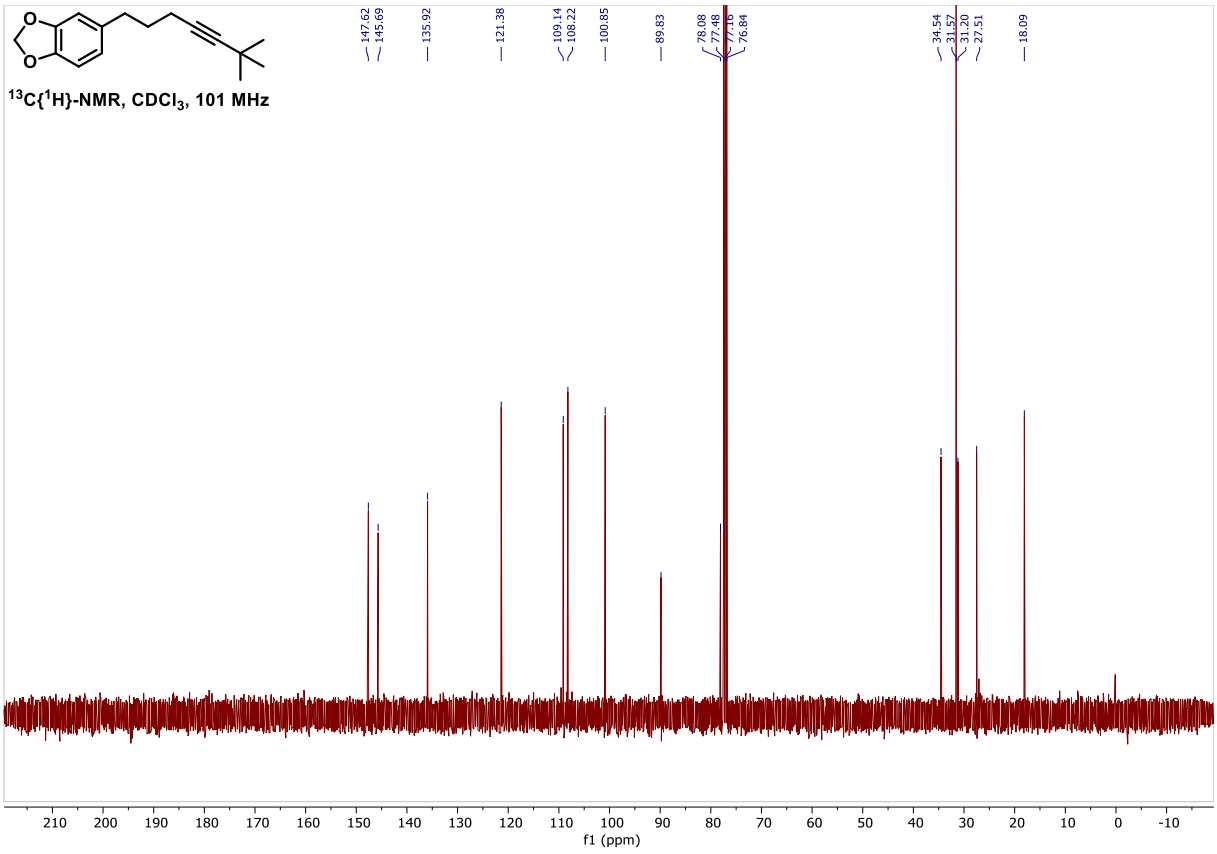
5-(3-Bromopropyl)benzo-1,3-dioxole (**3.19c**)



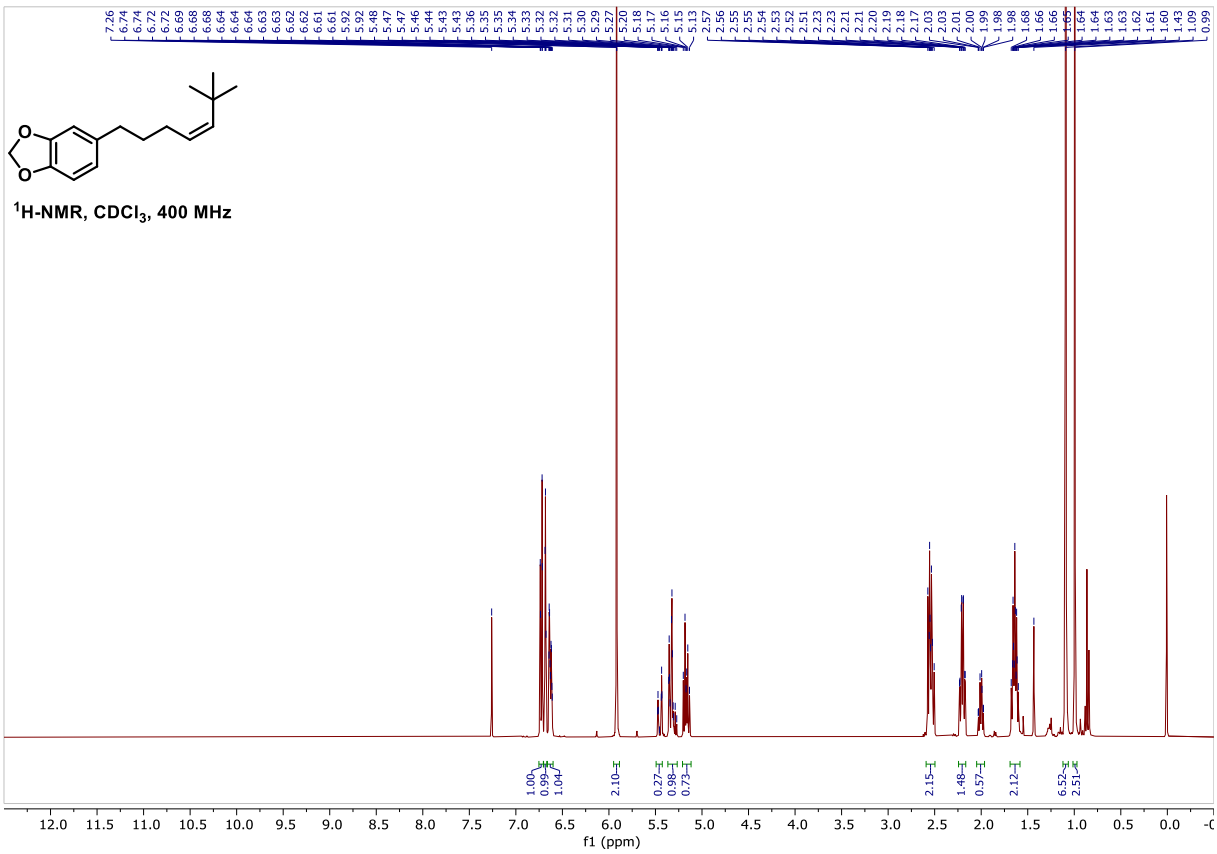


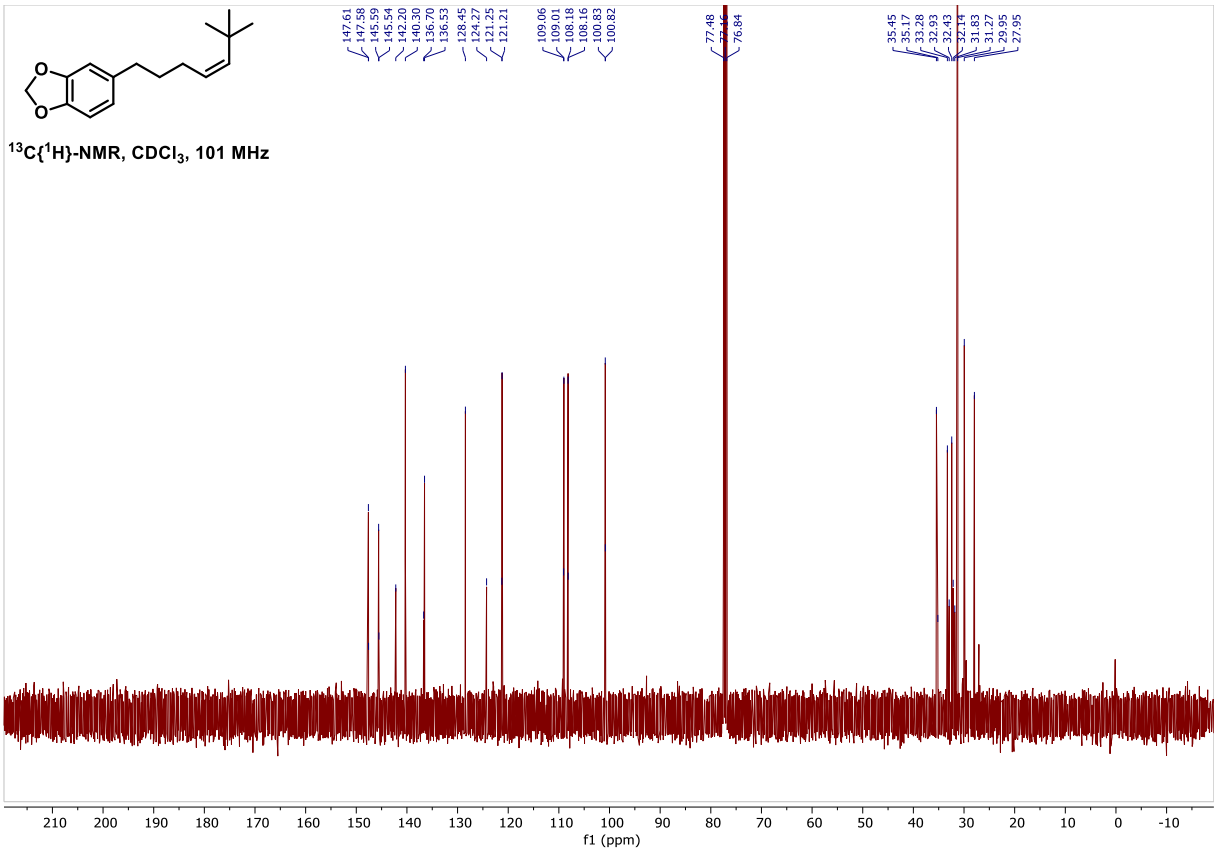
5-(6,6-Dimethylhept-4-yn-1-yl)benzo-1,3-dioxole (**3.20g**)



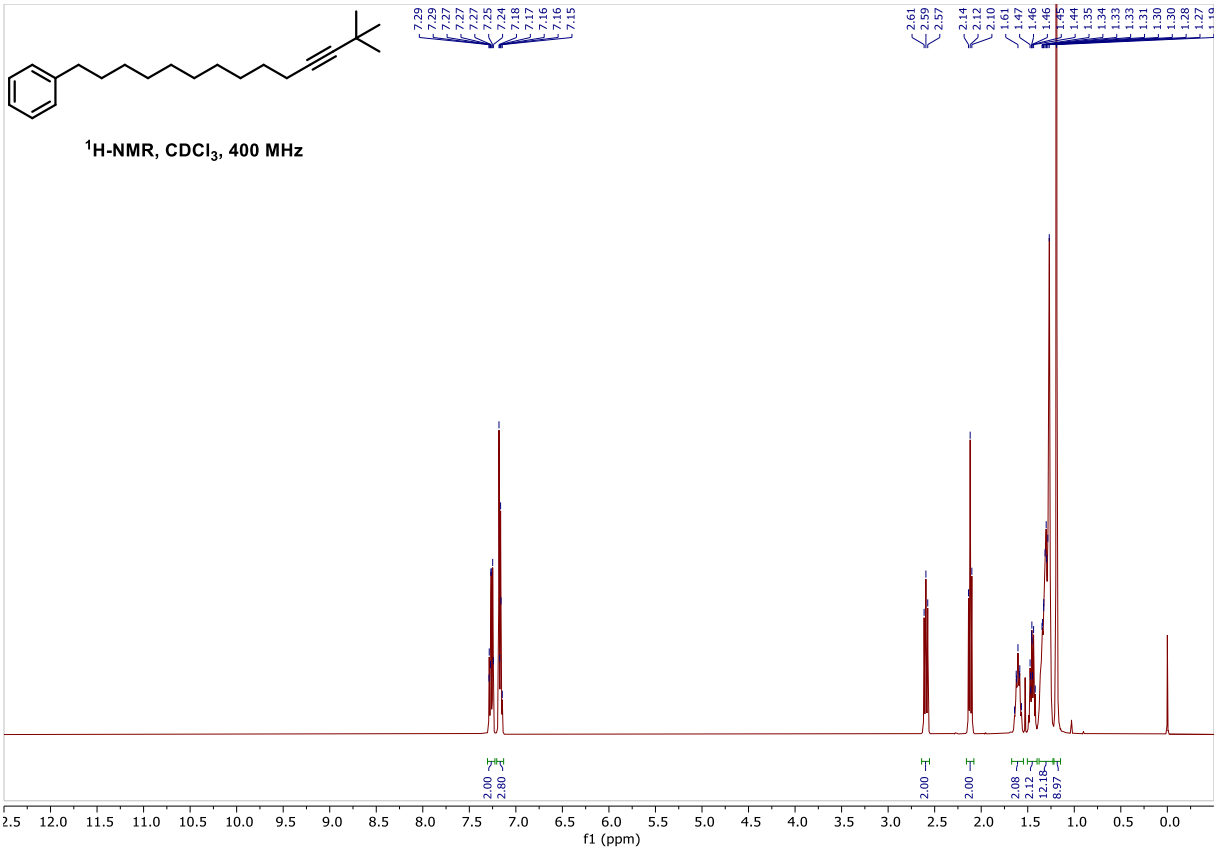


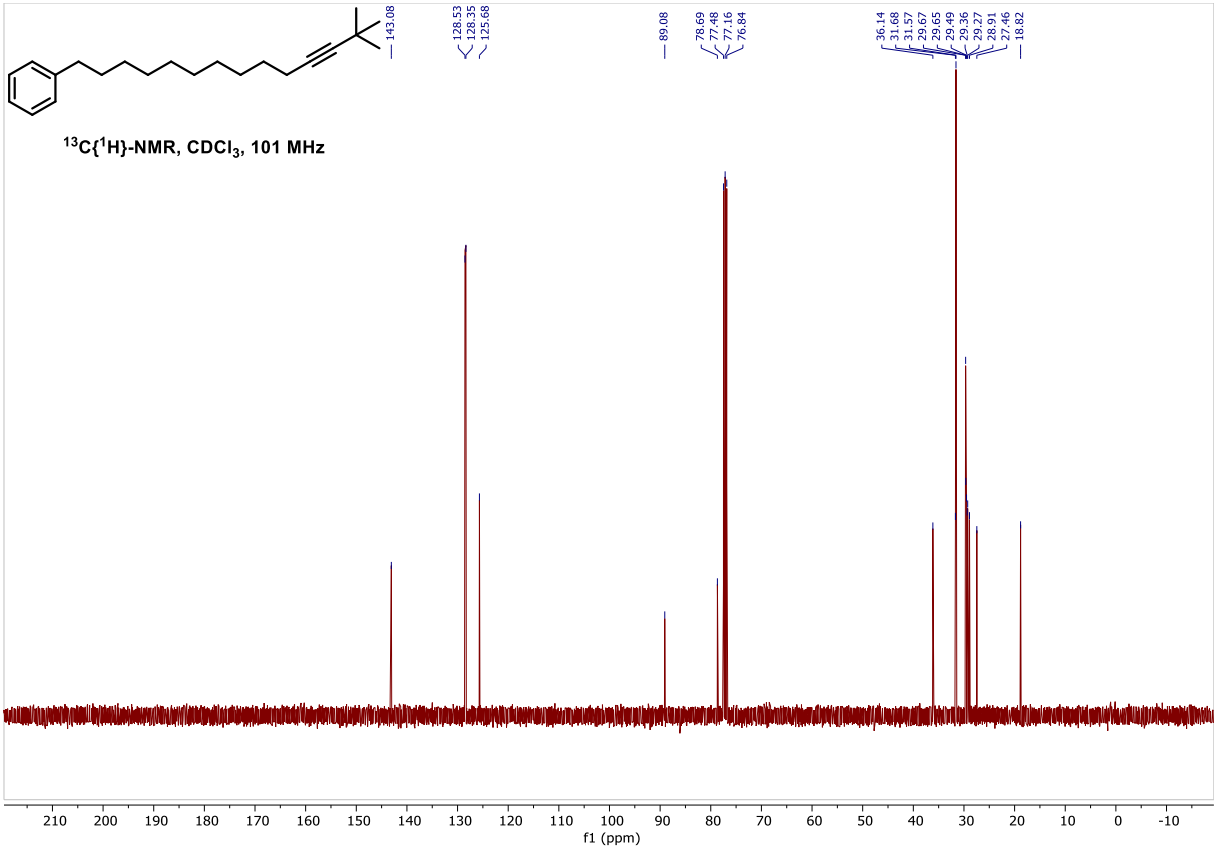
(*Z*)-5-(6,6-Dimethylhept-4-en-1-yl)benzo-1,3-dioxole (**3.1j**)



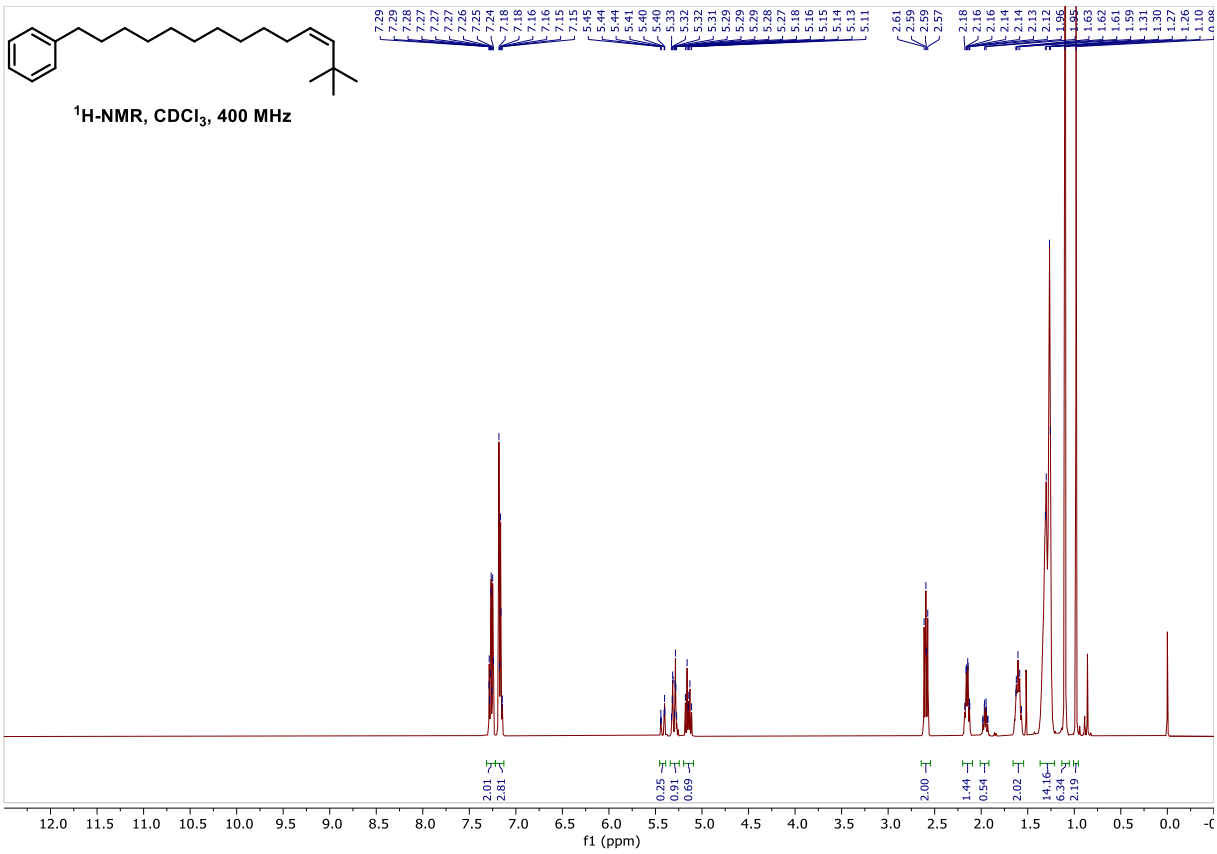


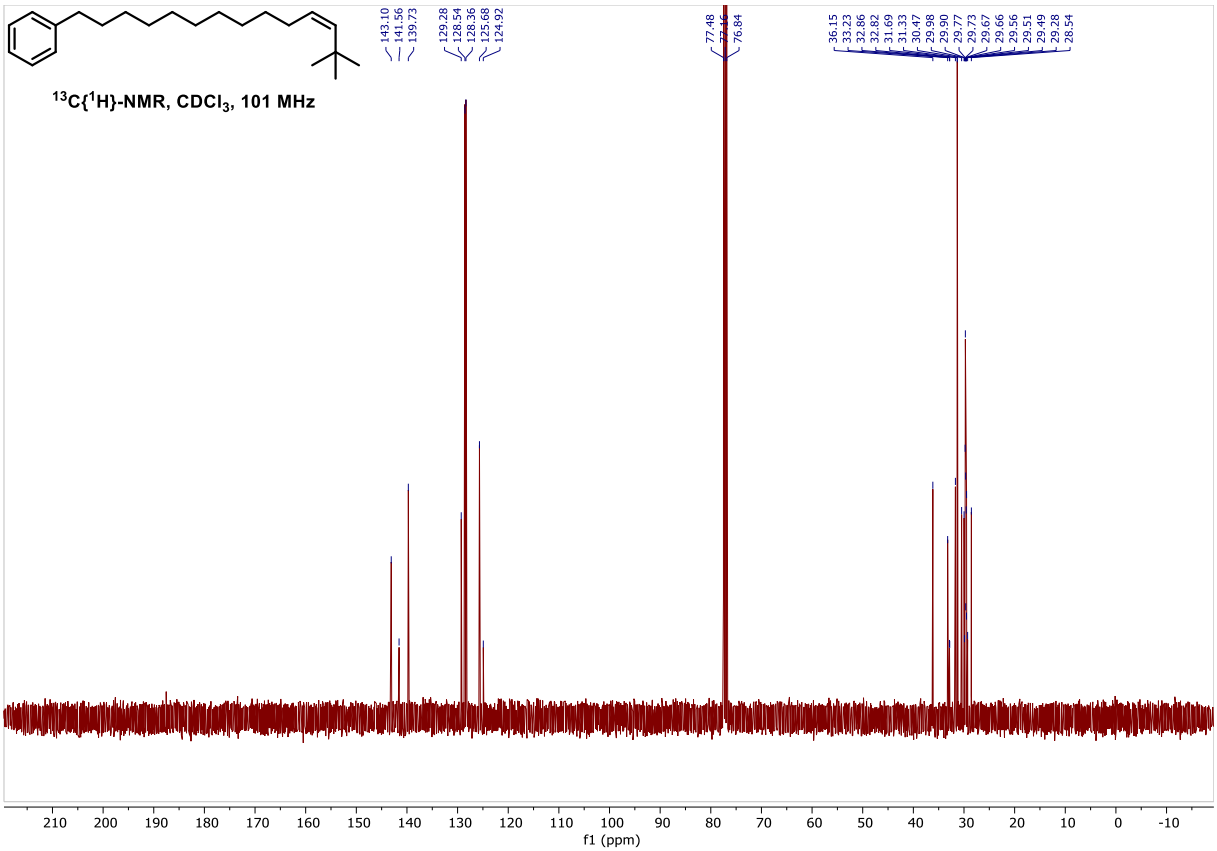
(13,13-Dimethyltetradec-11-yn-1-yl)benzene (**3.20h**)



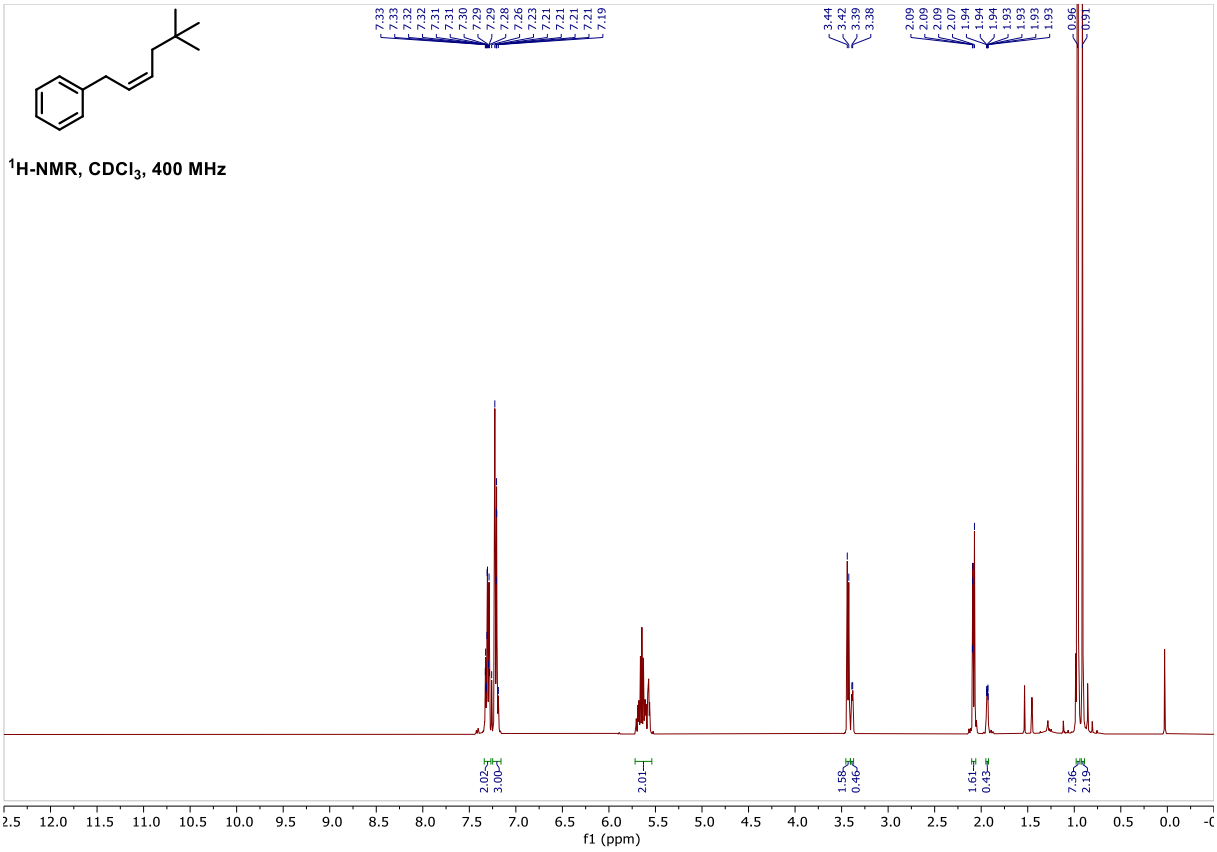


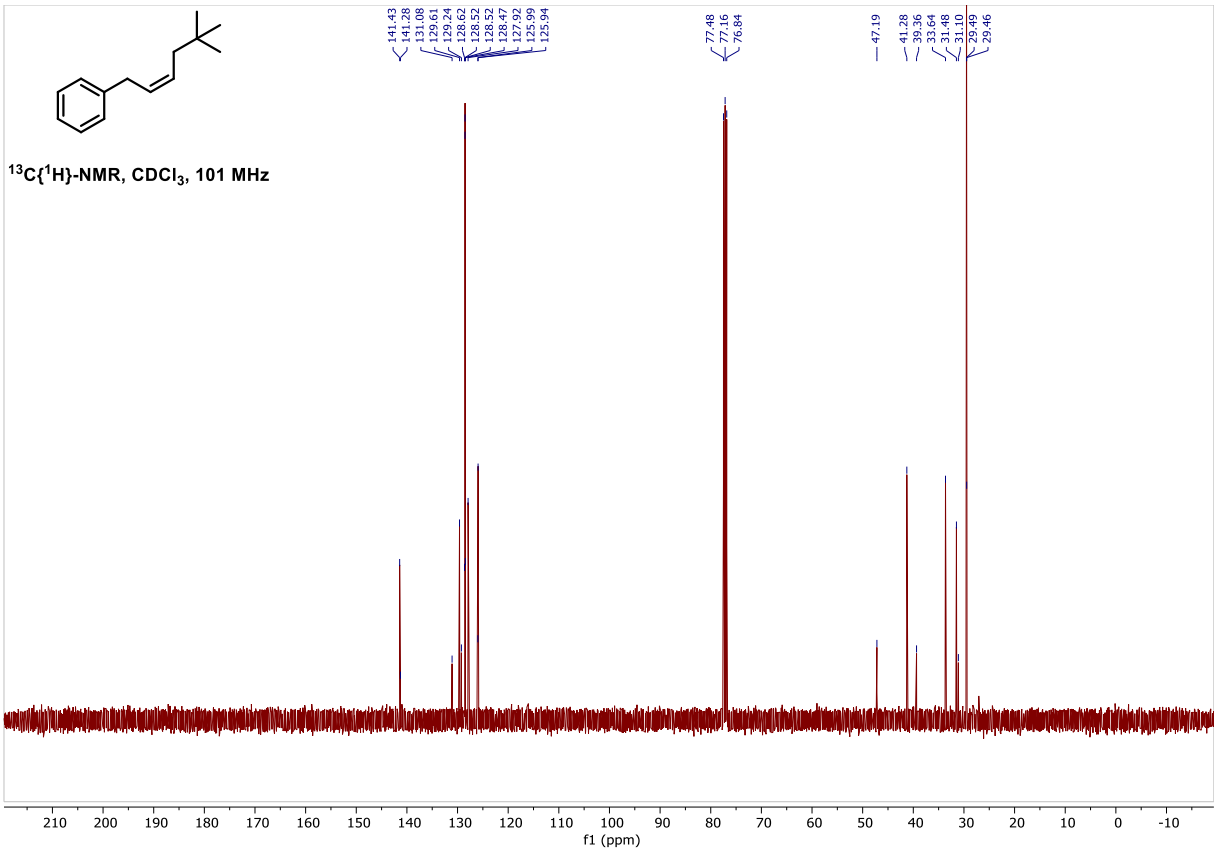
(*Z*)-(13,13-Dimethyltetradec-11-en-1-yl)benzene (**3.1k**)



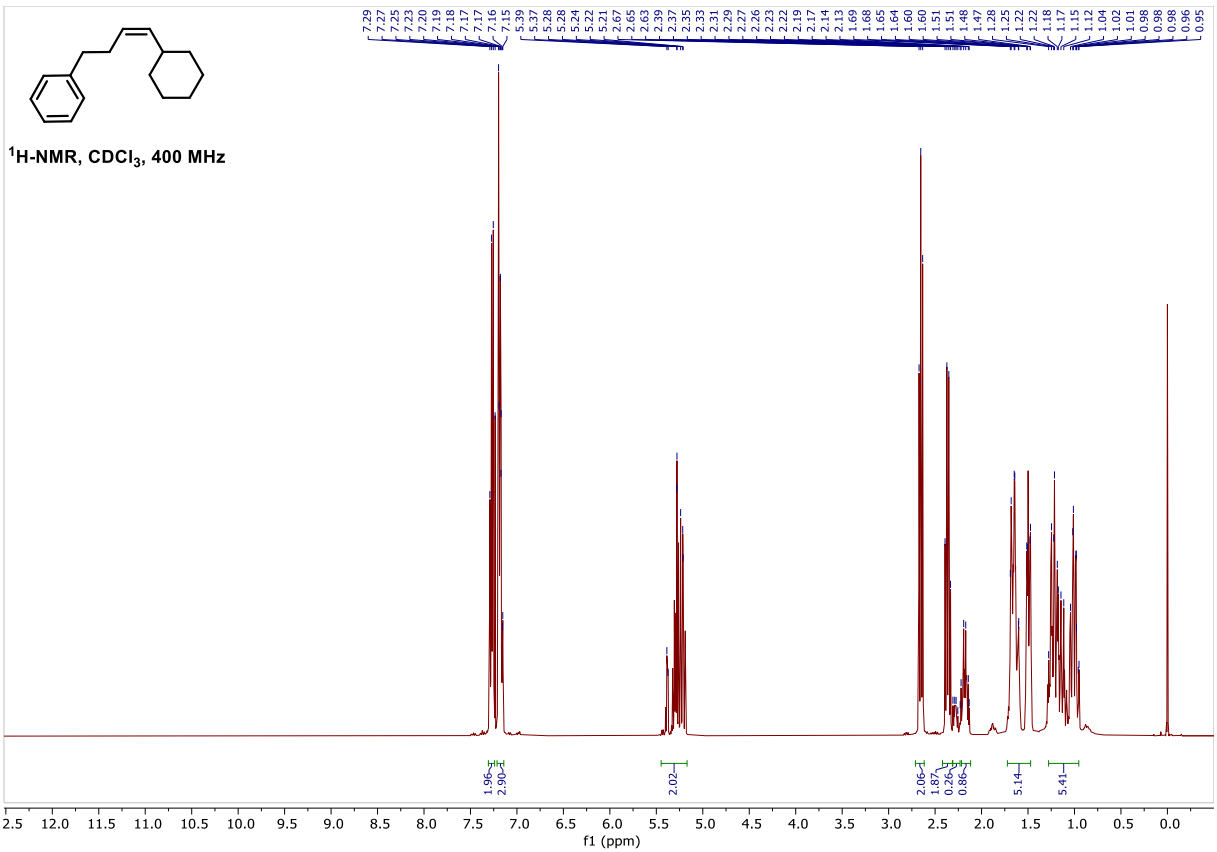


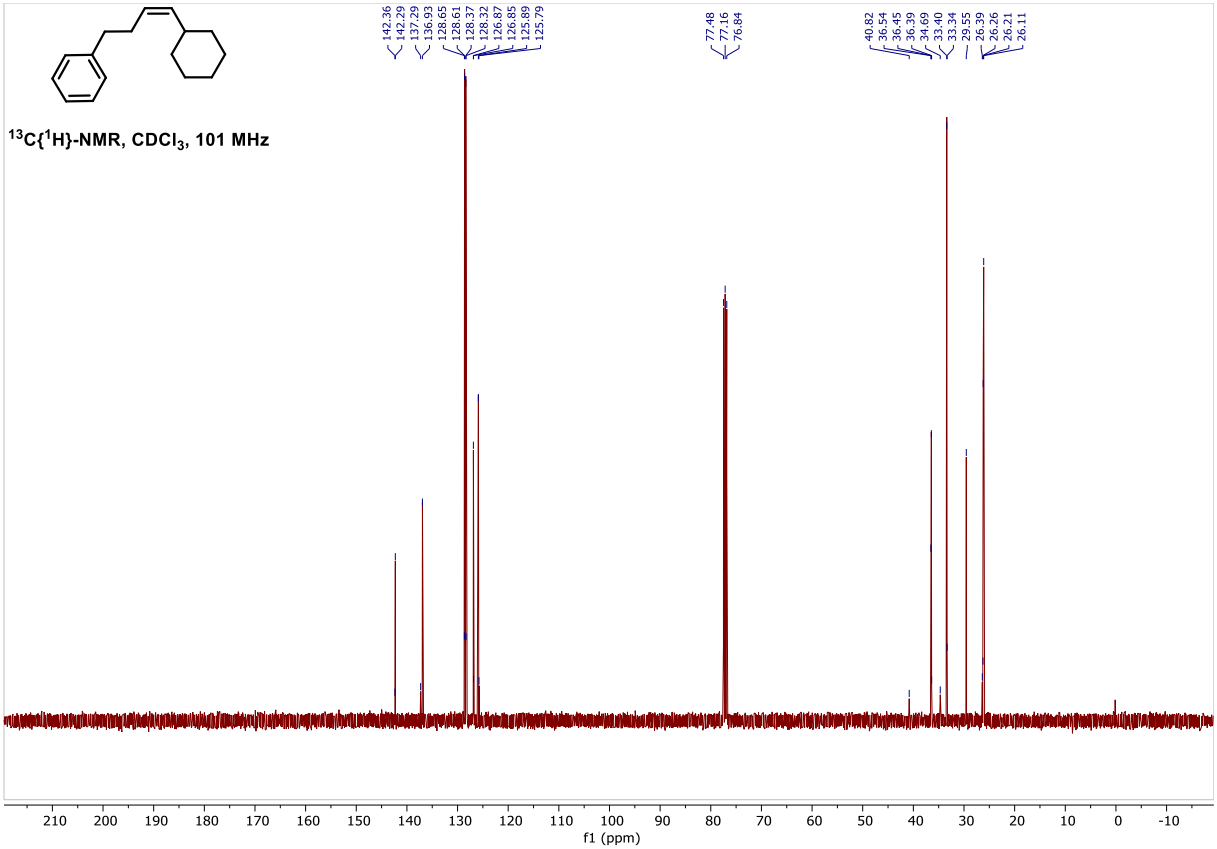
(*Z*)-(5,5-Dimethylhex-2-en-1-yl)benzene (**3.1l**)



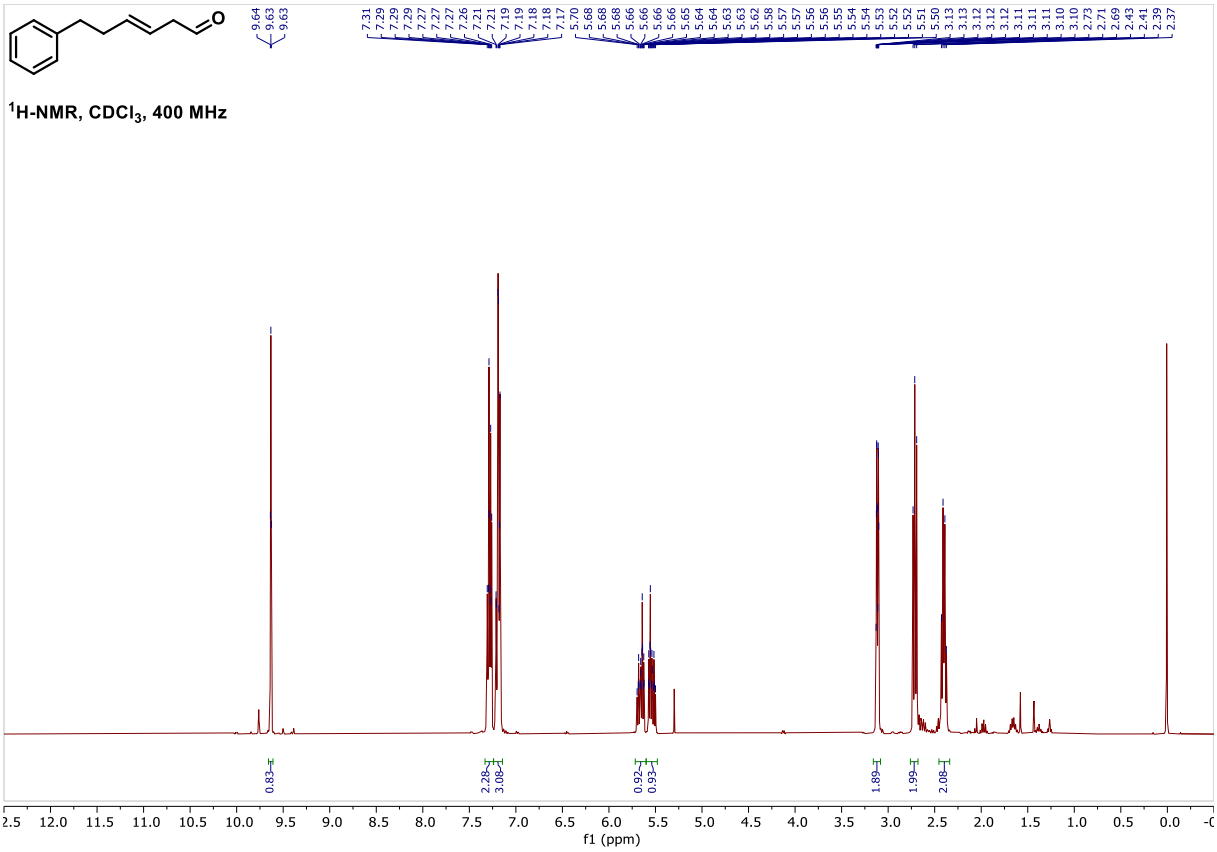


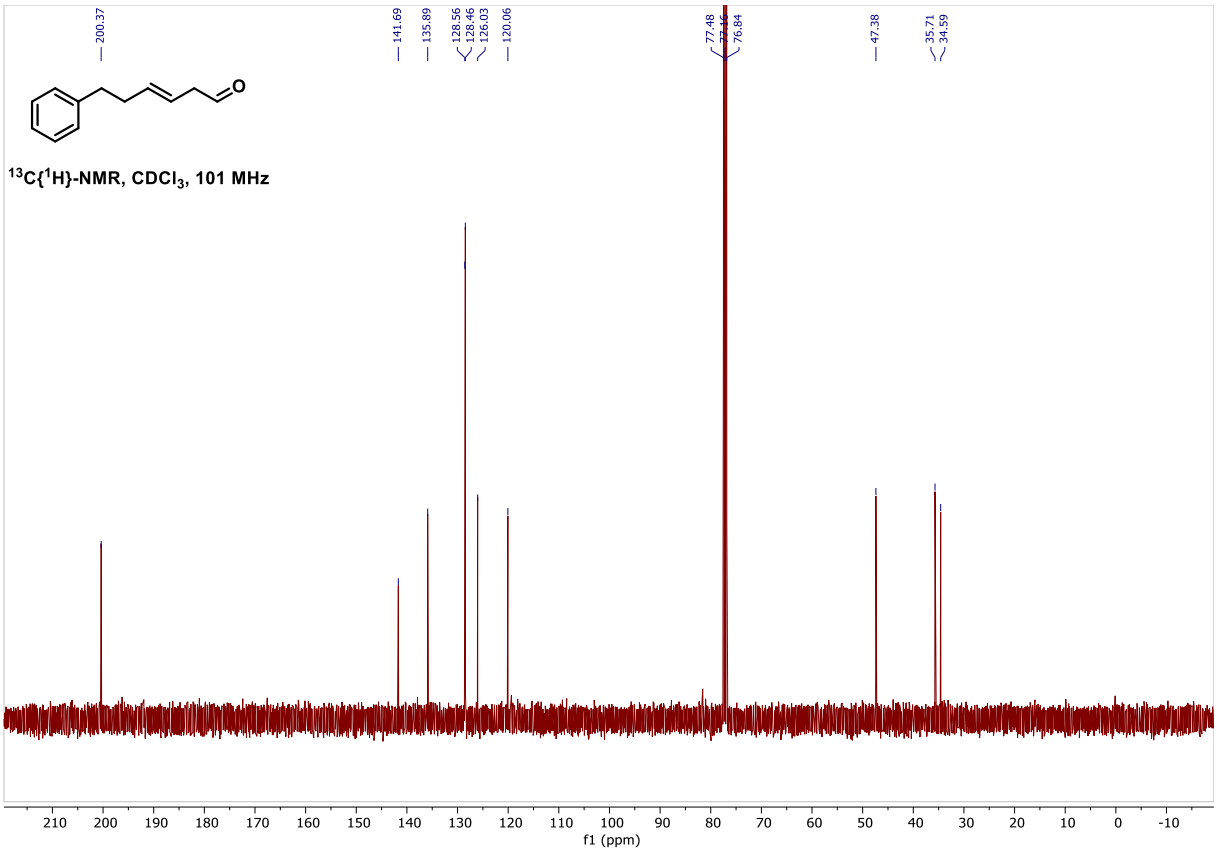
(*Z*)-(4-Cyclohexylbut-3-en-1-yl)benzene (**3.1m**)



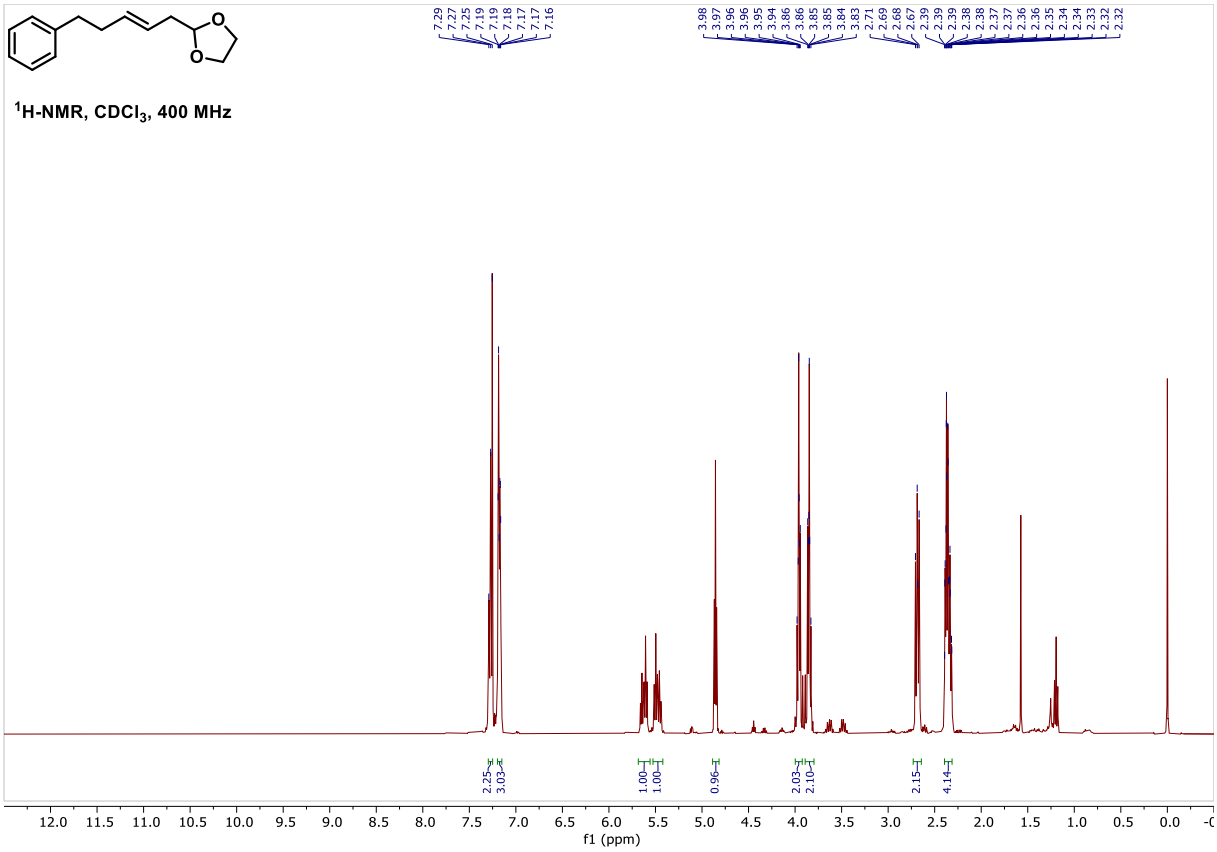


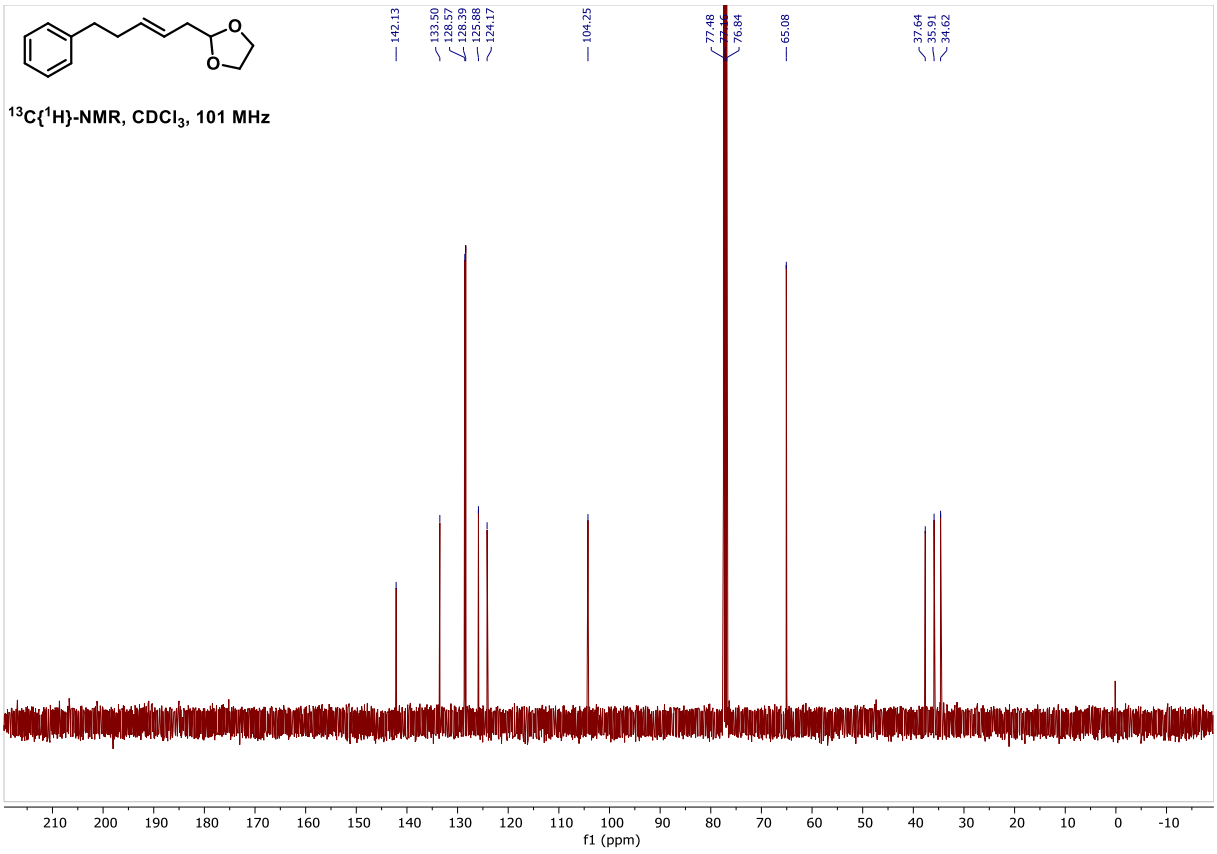
(*E*)-6-Phenylhex-3-enal (**3.21**)



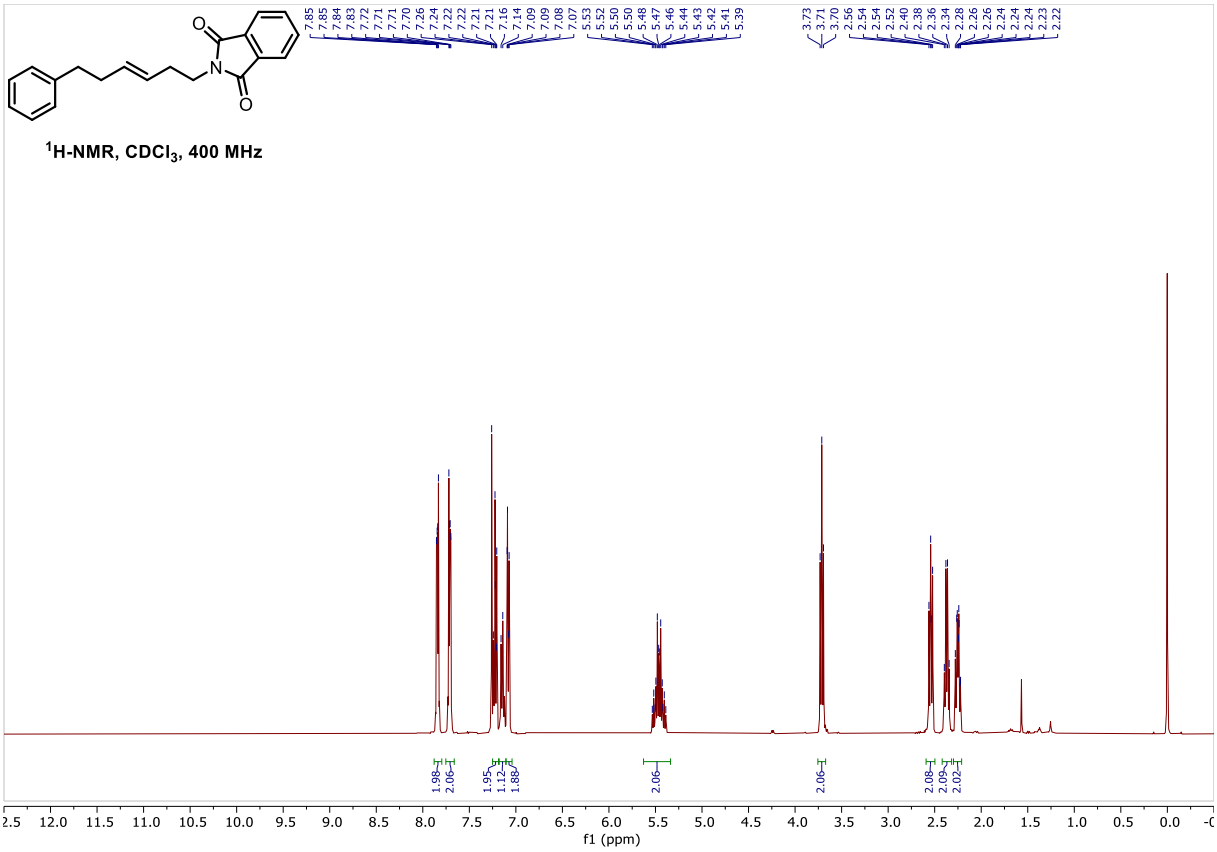


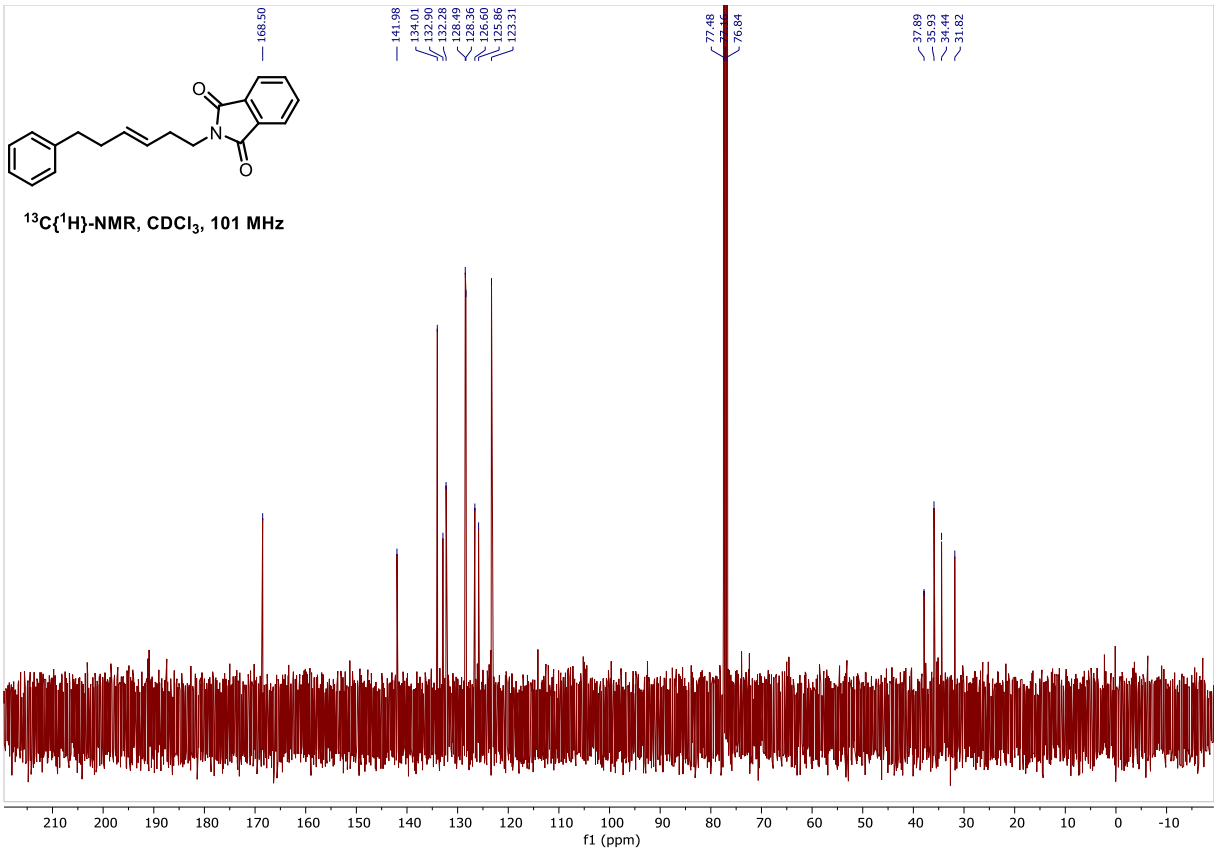
(*E*)-2-(5-Phenylpent-2-en-1-yl)-1,3-dioxolane (**3.1n**)



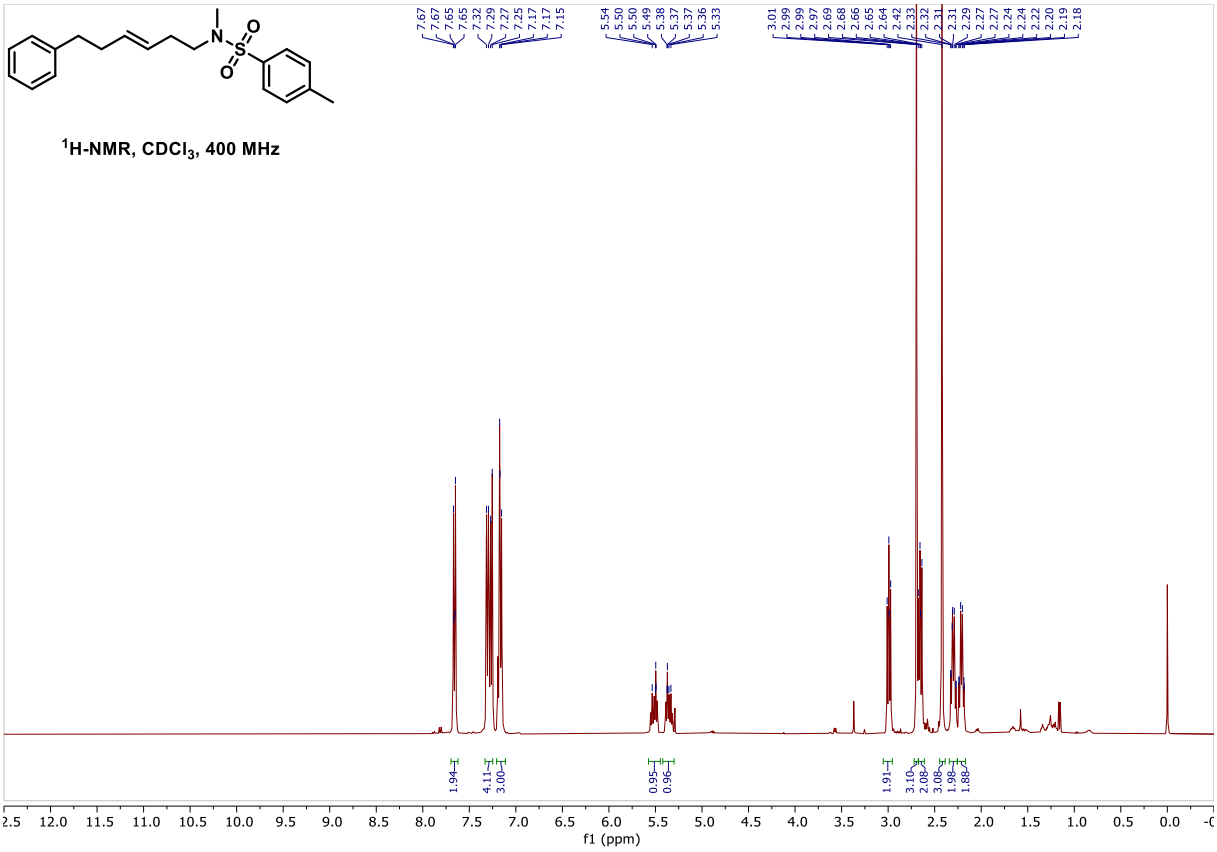


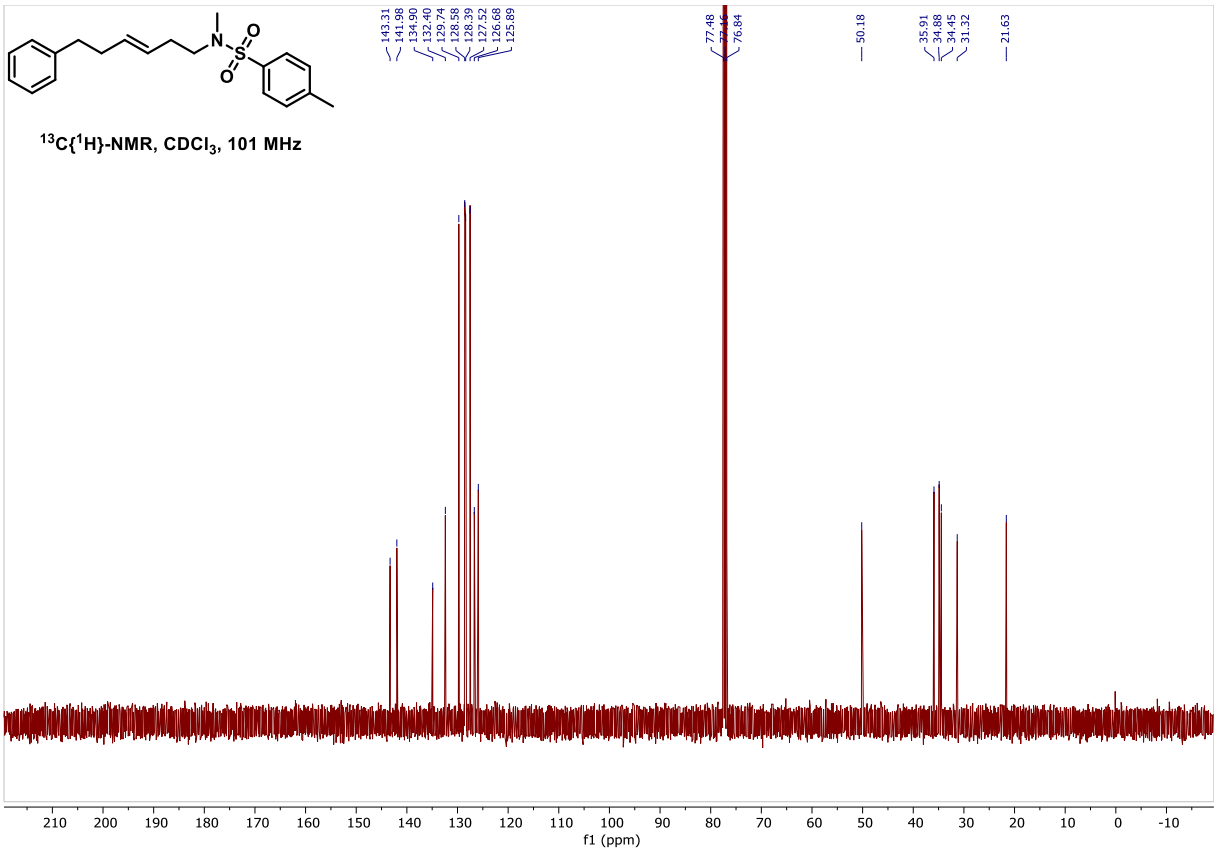
(*E*)-2-(6-Phenylhex-3-en-1-yl)isoindoline-1,3-dione (**3.1o**)



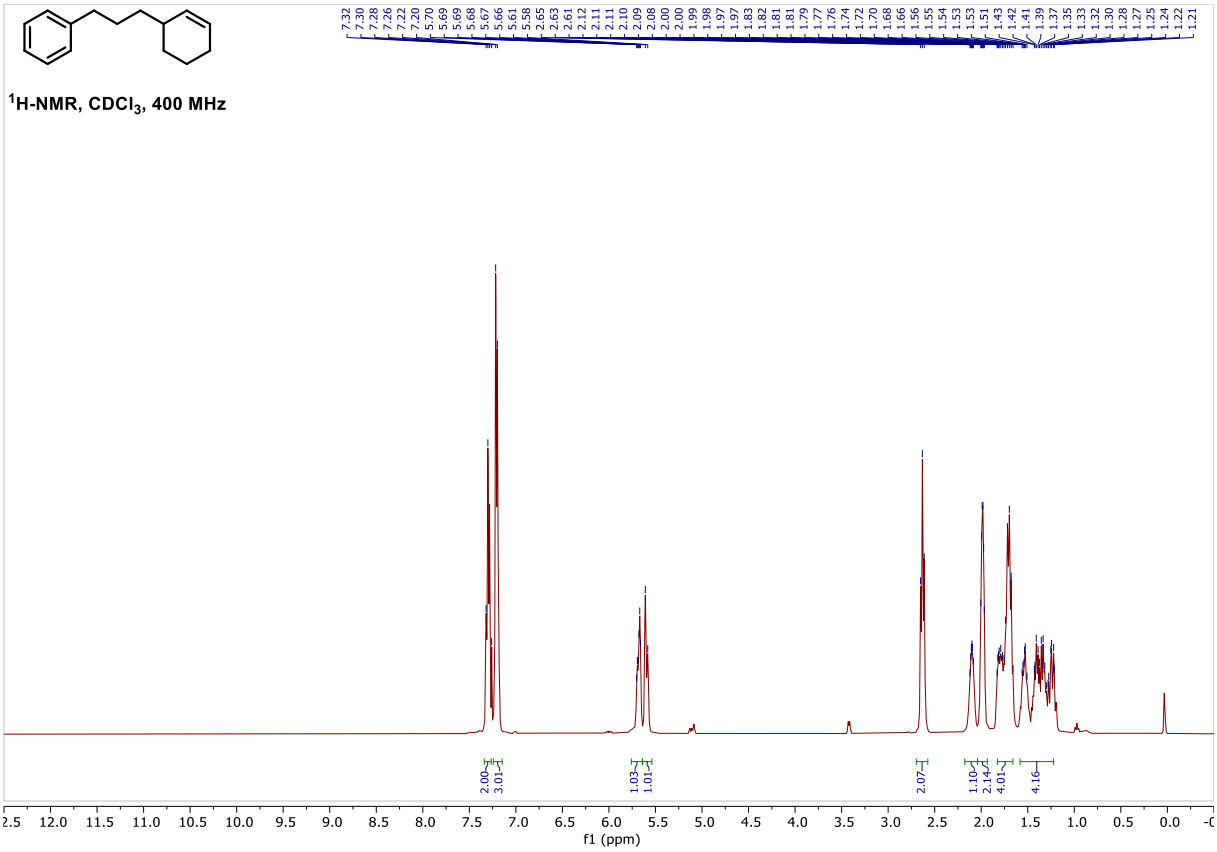


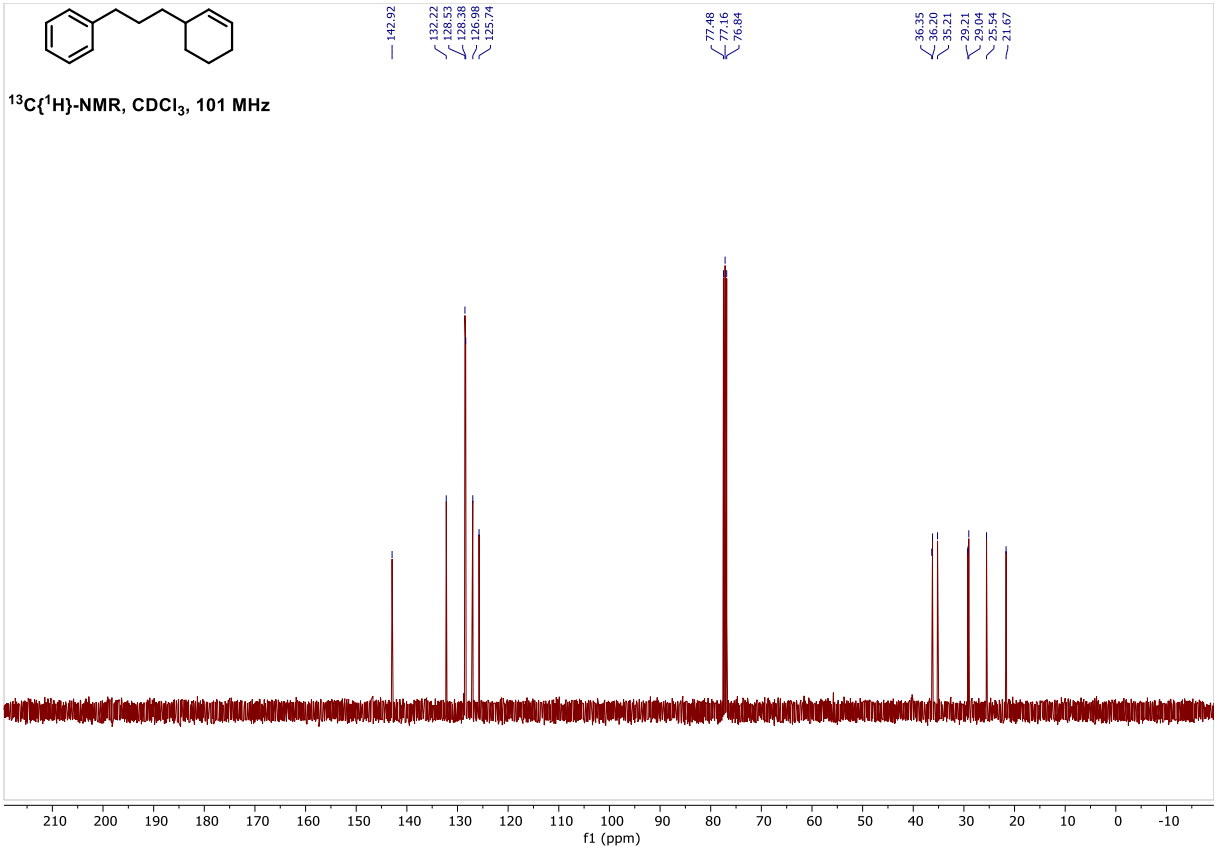
(*E*)-*N*,4-Dimethyl-N-(6-phenylhex-3-en-1-yl)benzenesulfonamide (**3.1p**)



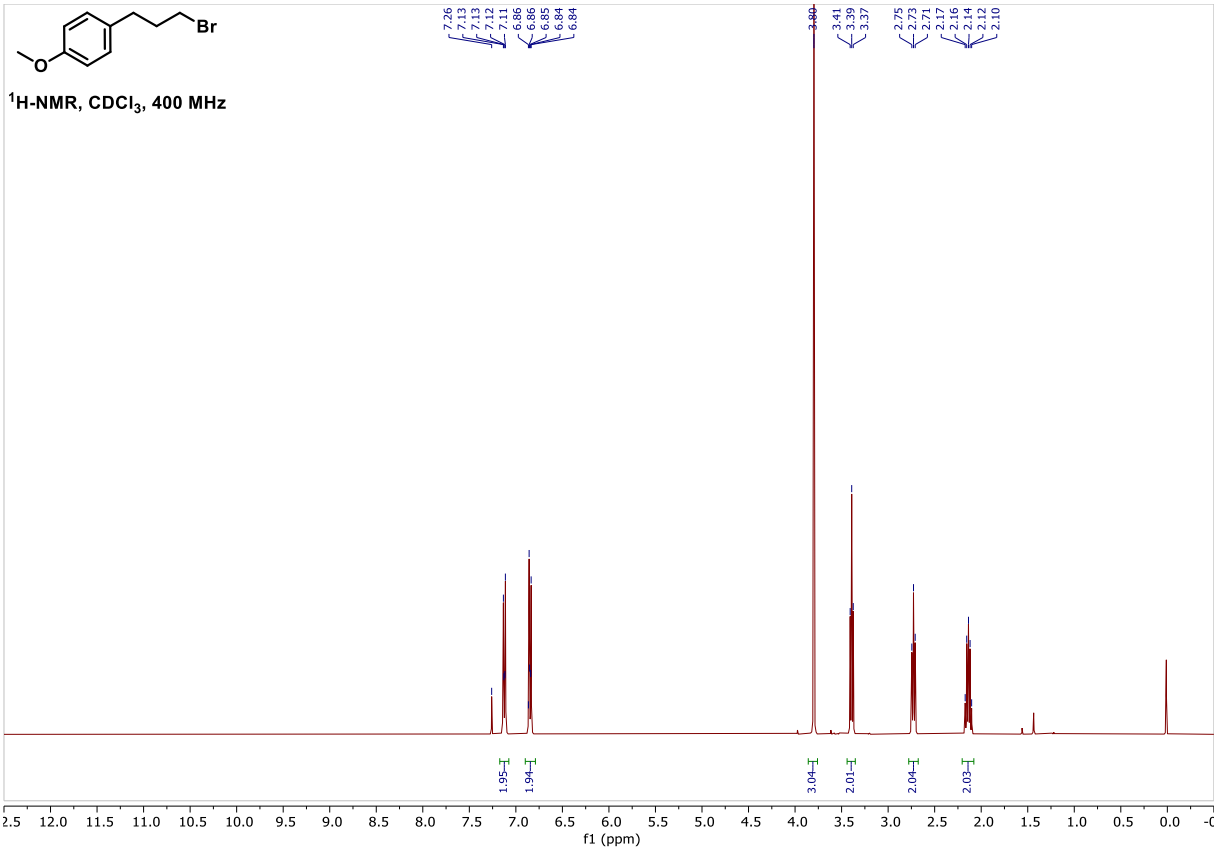


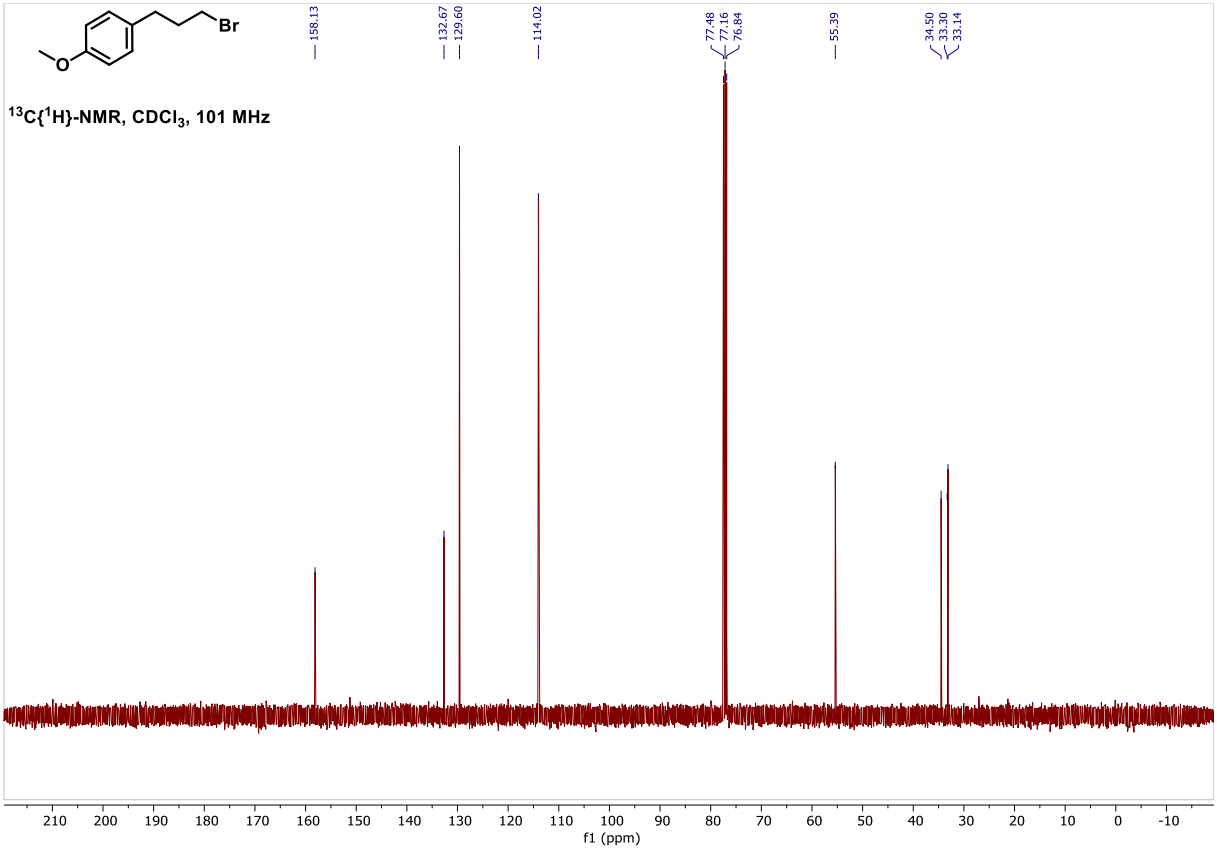
(3-(Cyclohex-2-en-1-yl)propyl)benzene (**3.1q**)



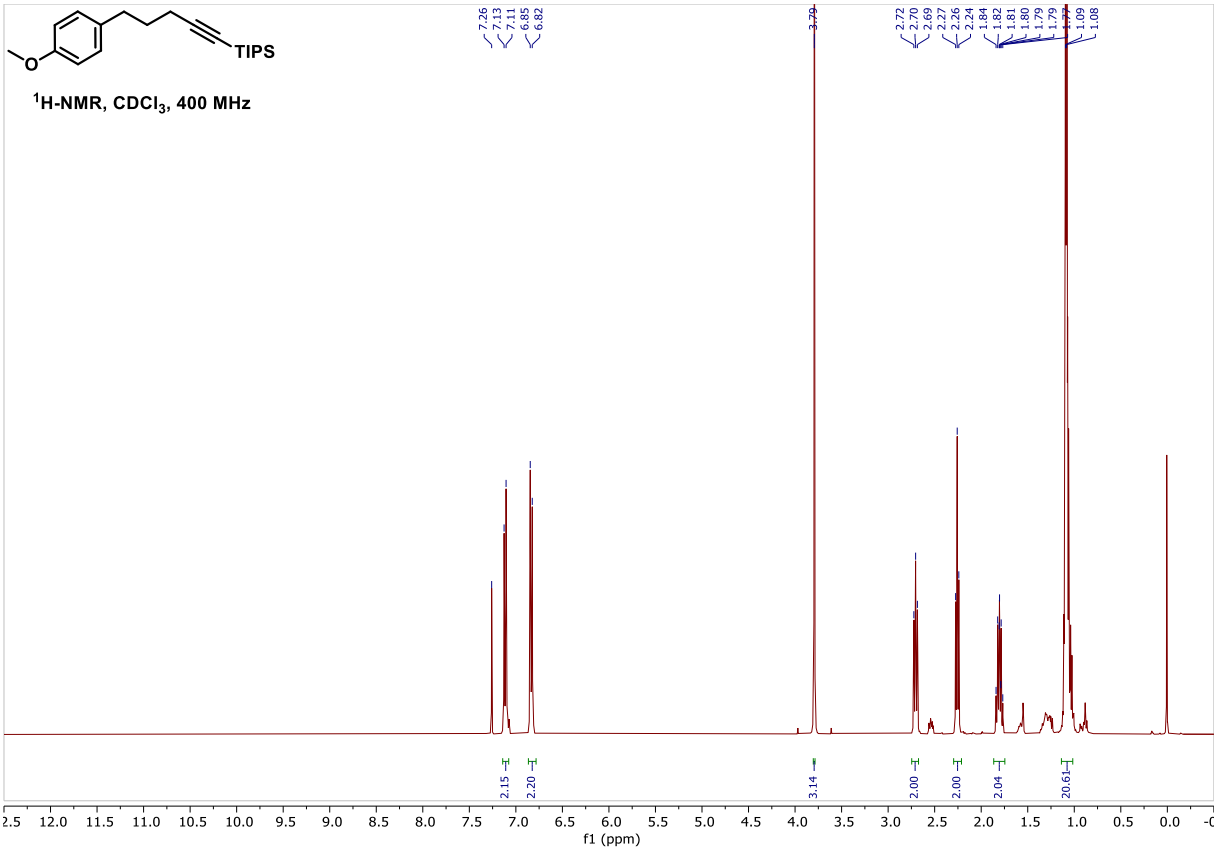


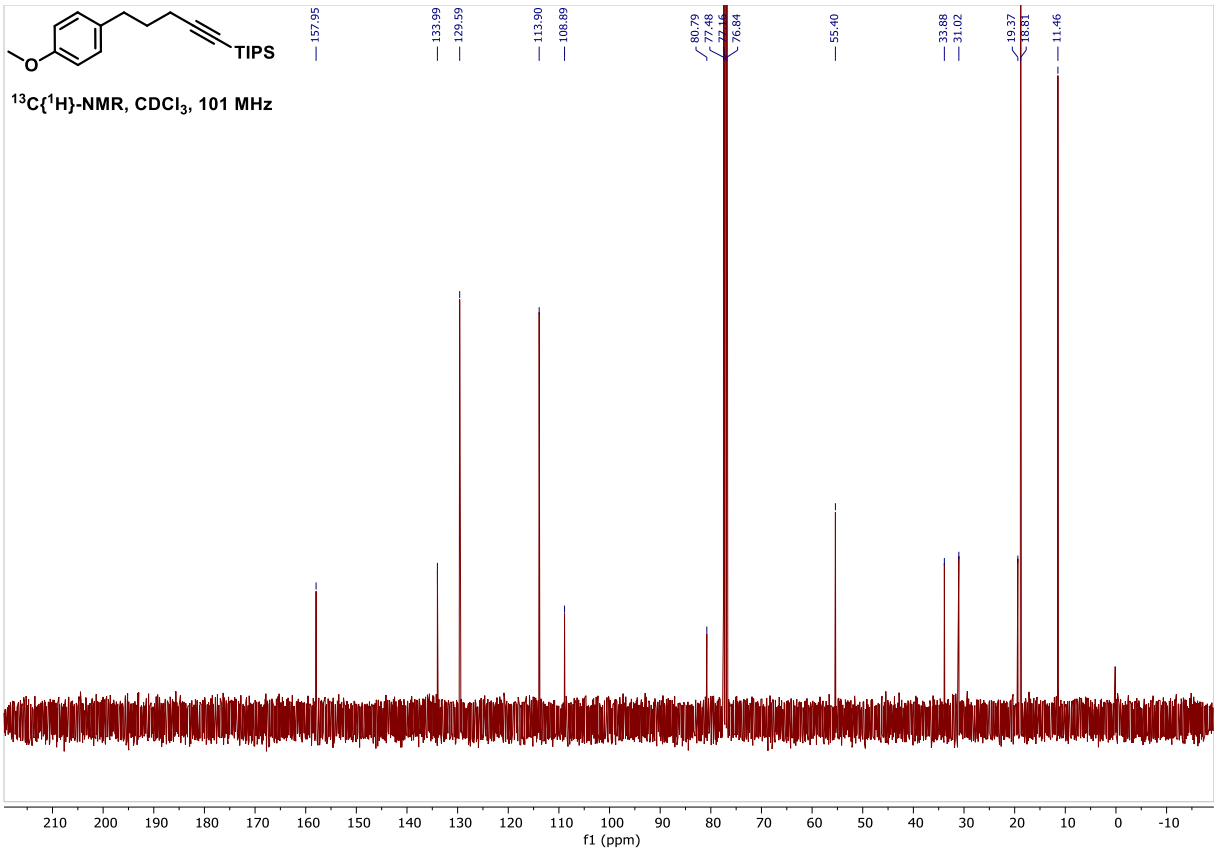
1-(3-Bromopropyl)-4-methoxybenzene (**3.18d**)



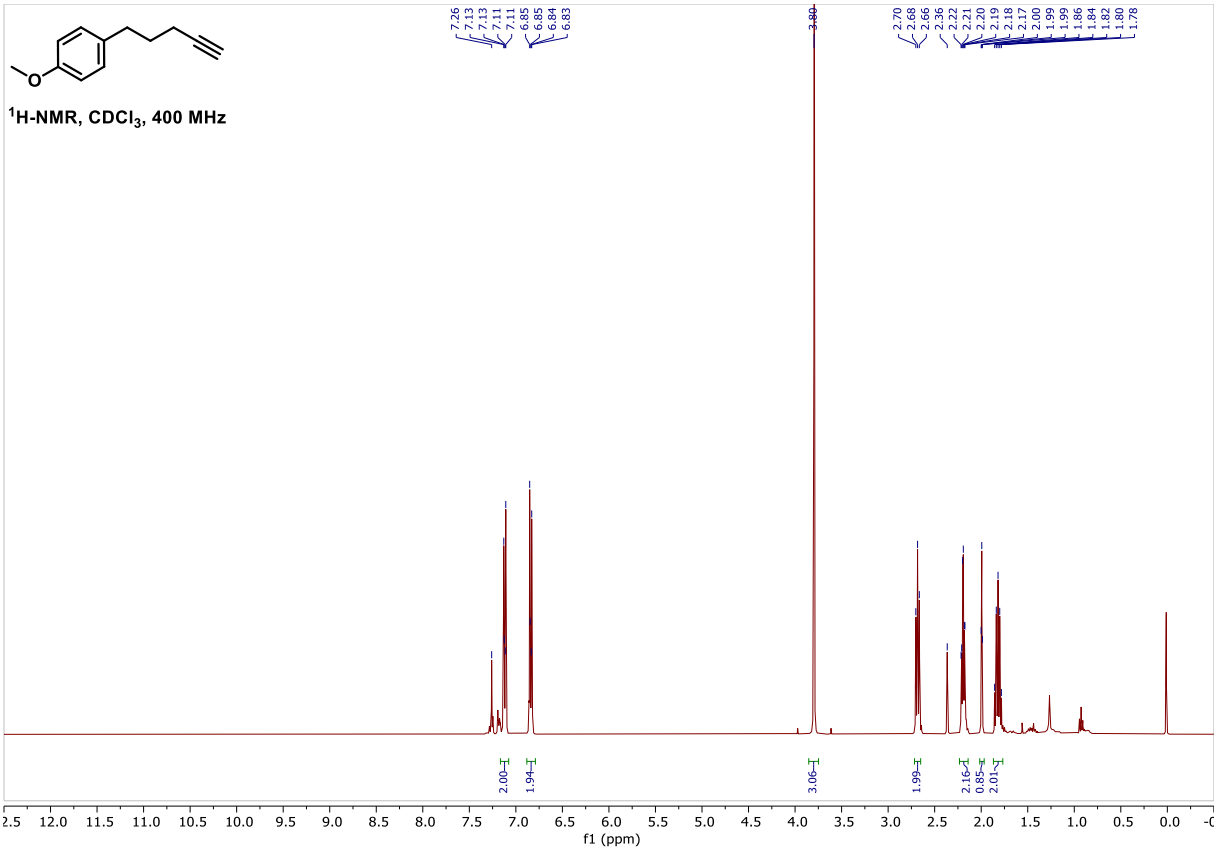


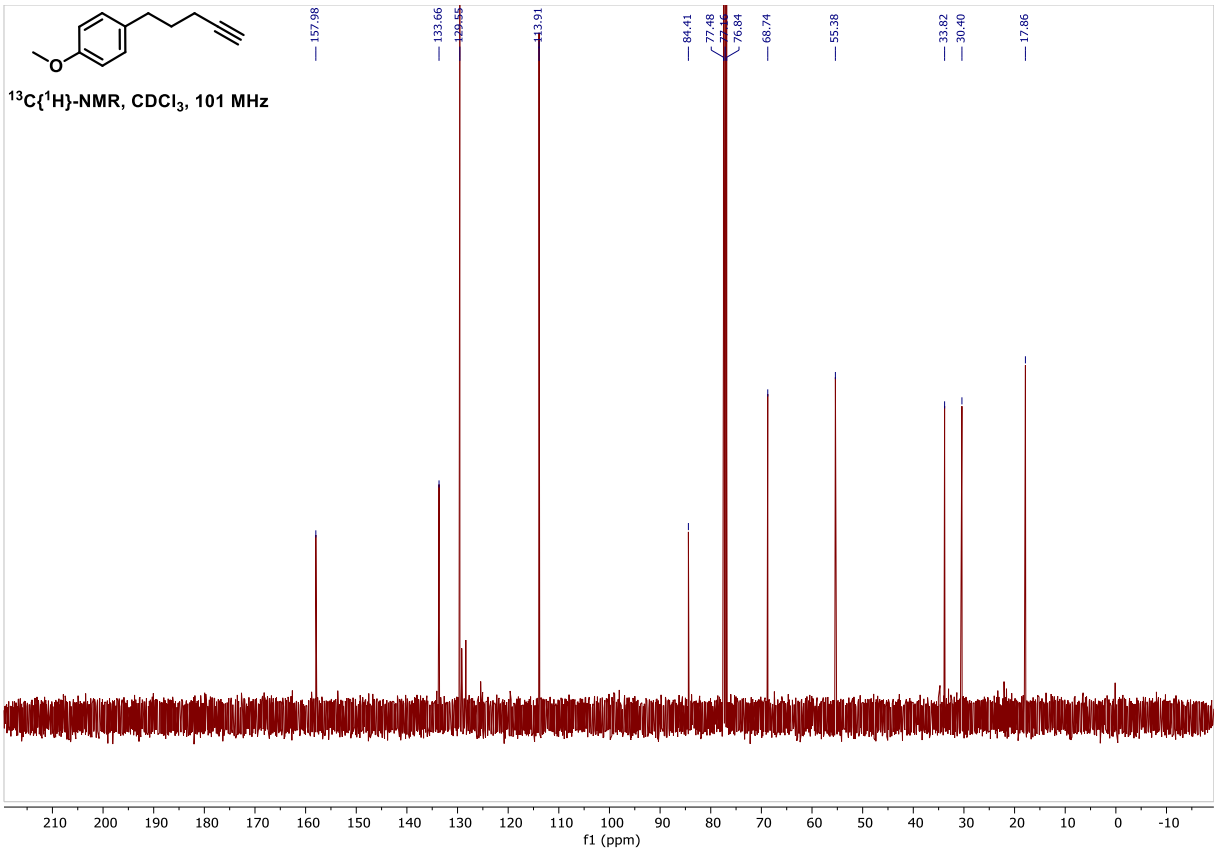
Tri*iso*propyl(5-(4-methoxyphenyl)pent-1-yn-1-yl)silane (**3.26**)



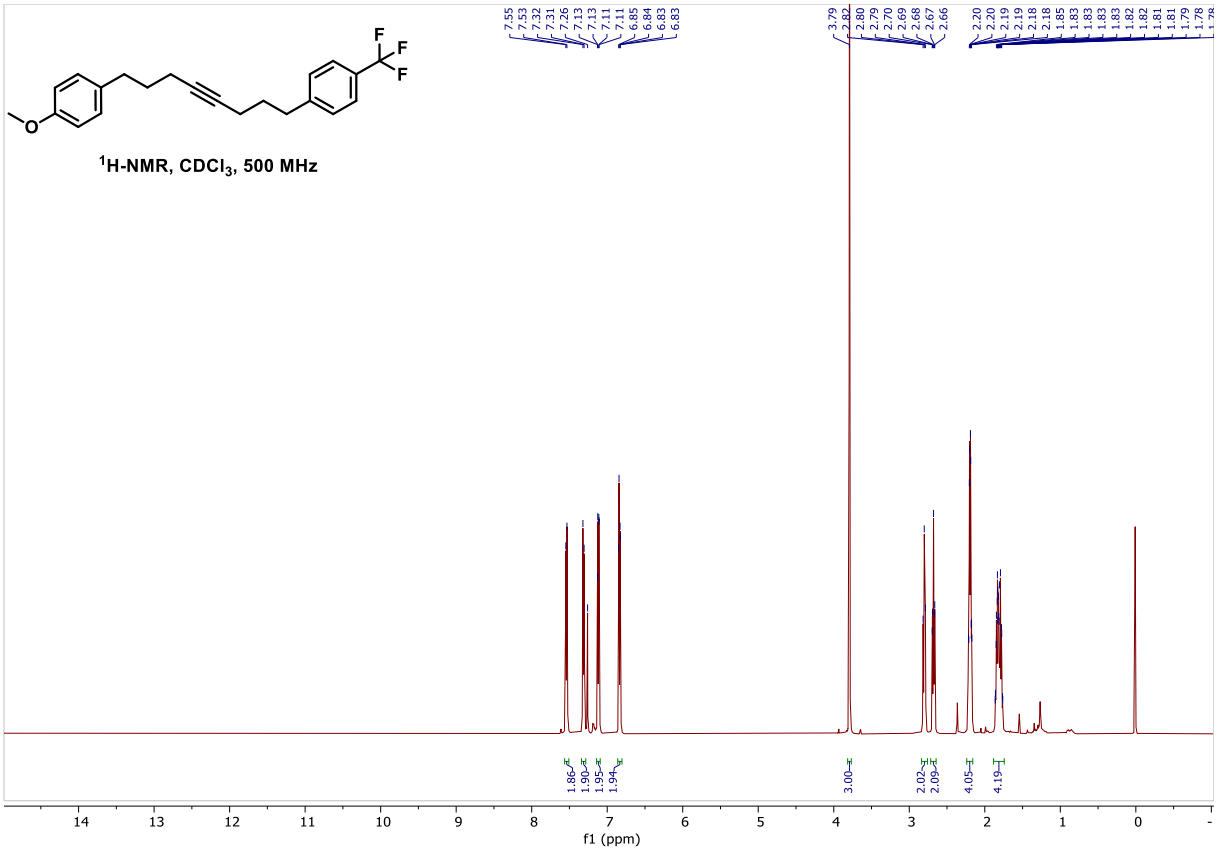


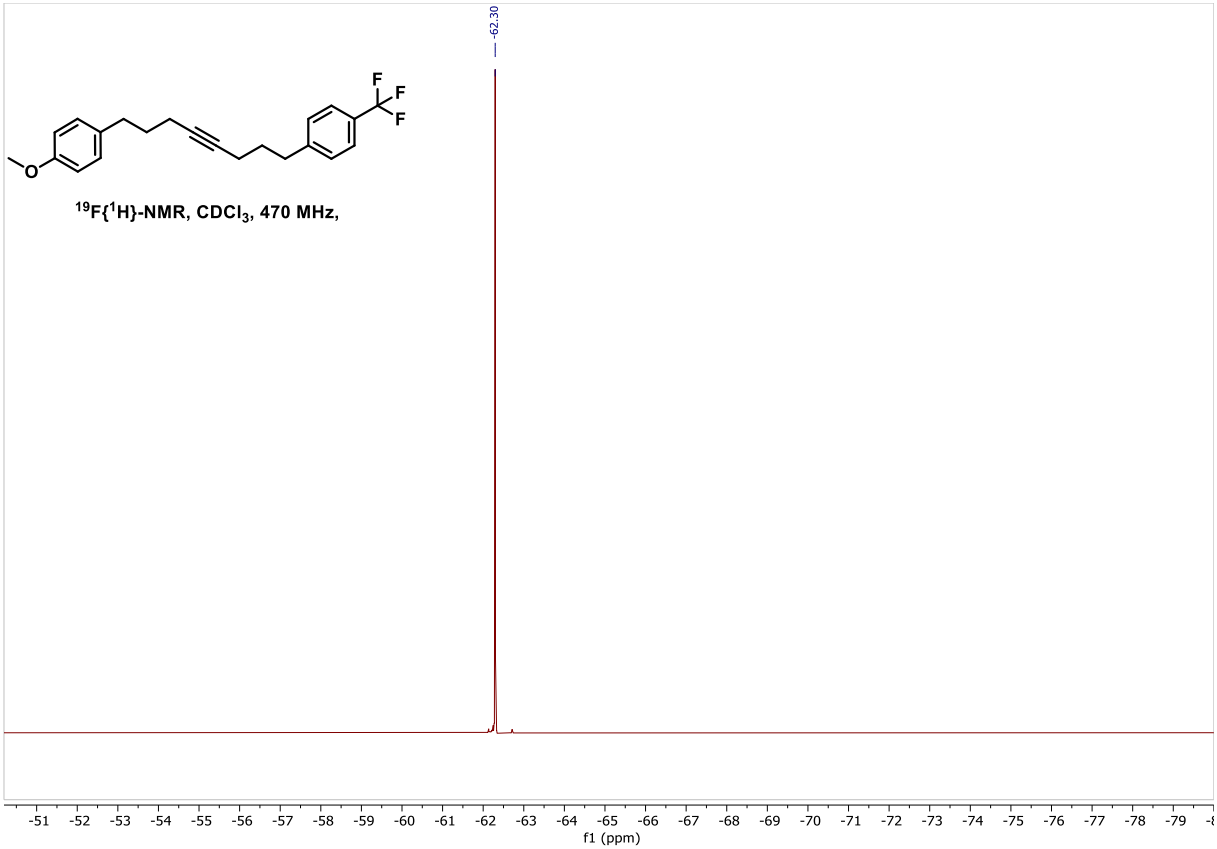
1-Methoxy-4-(pent-4-yn-1-yl)benzene (**3.27**)

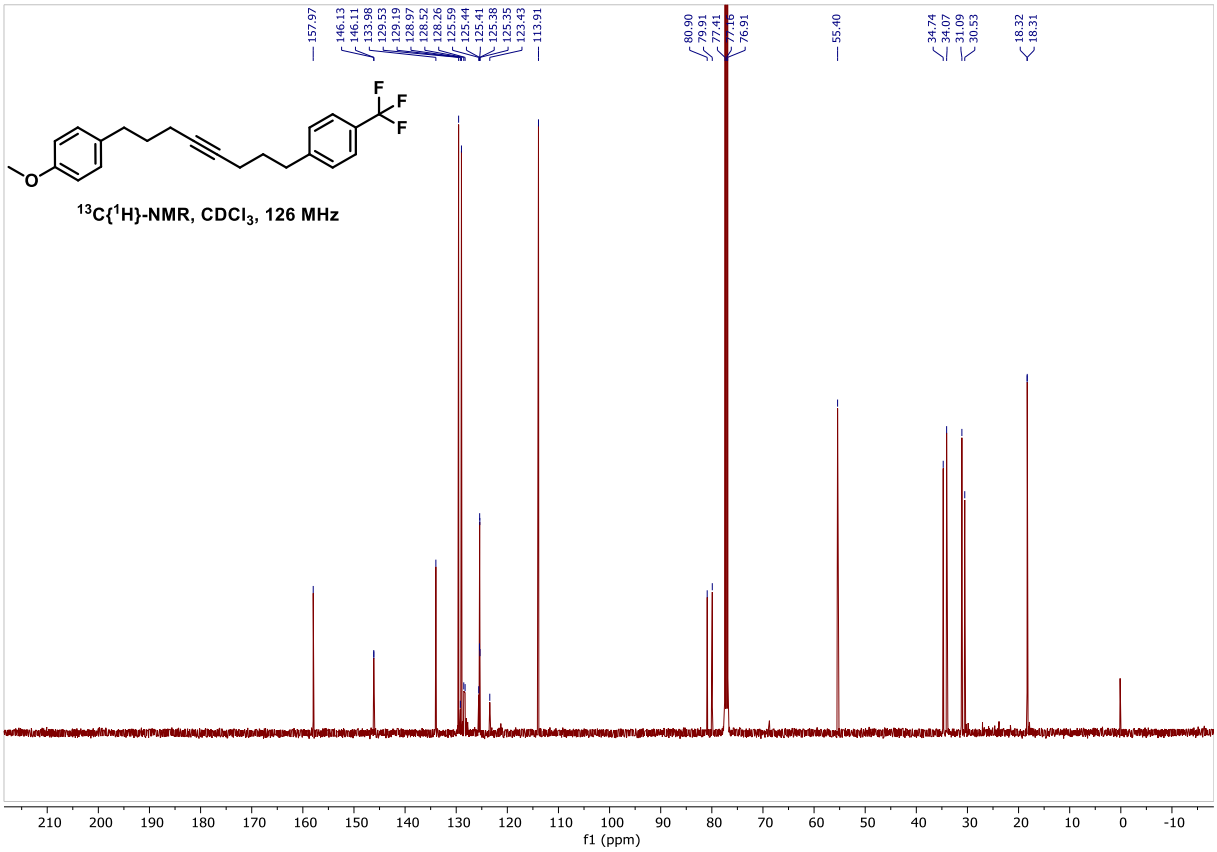




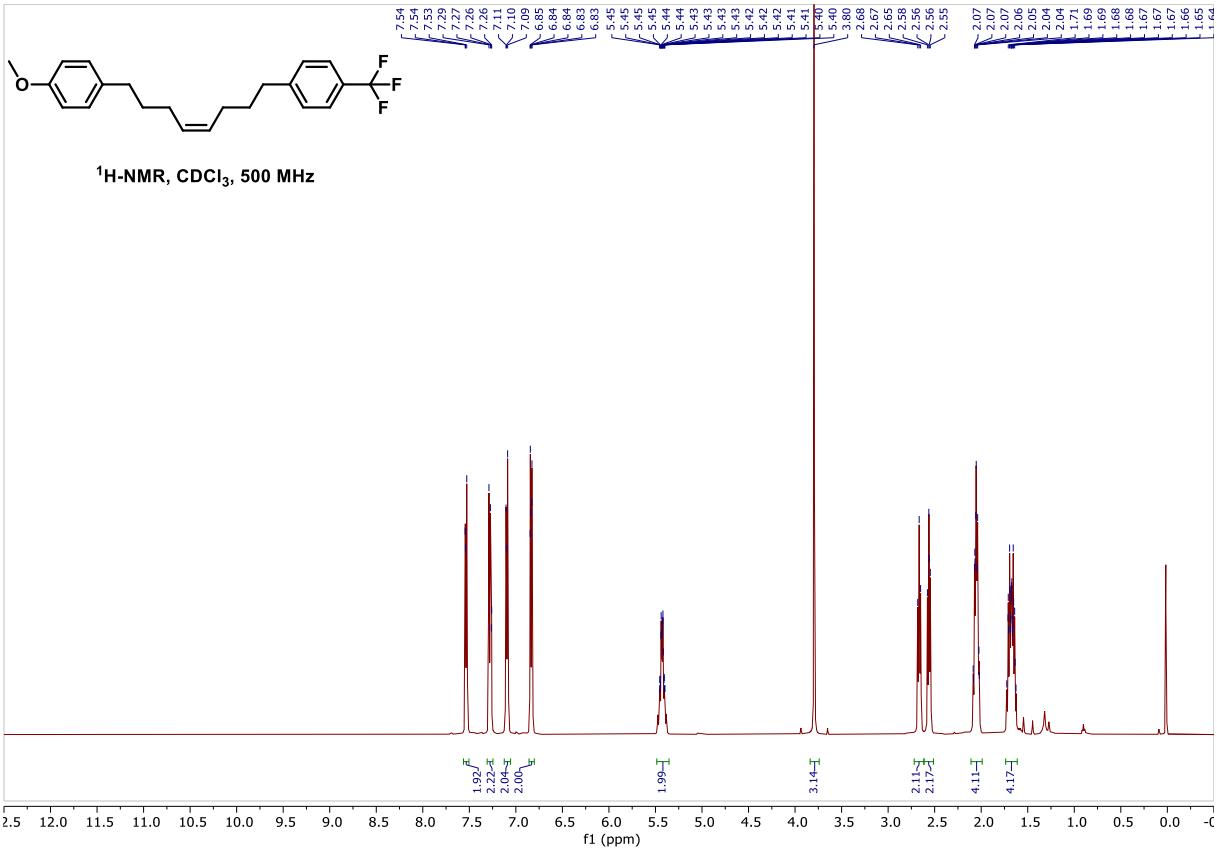
1-Methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-yn-1-yl)benzene (**3.28**)

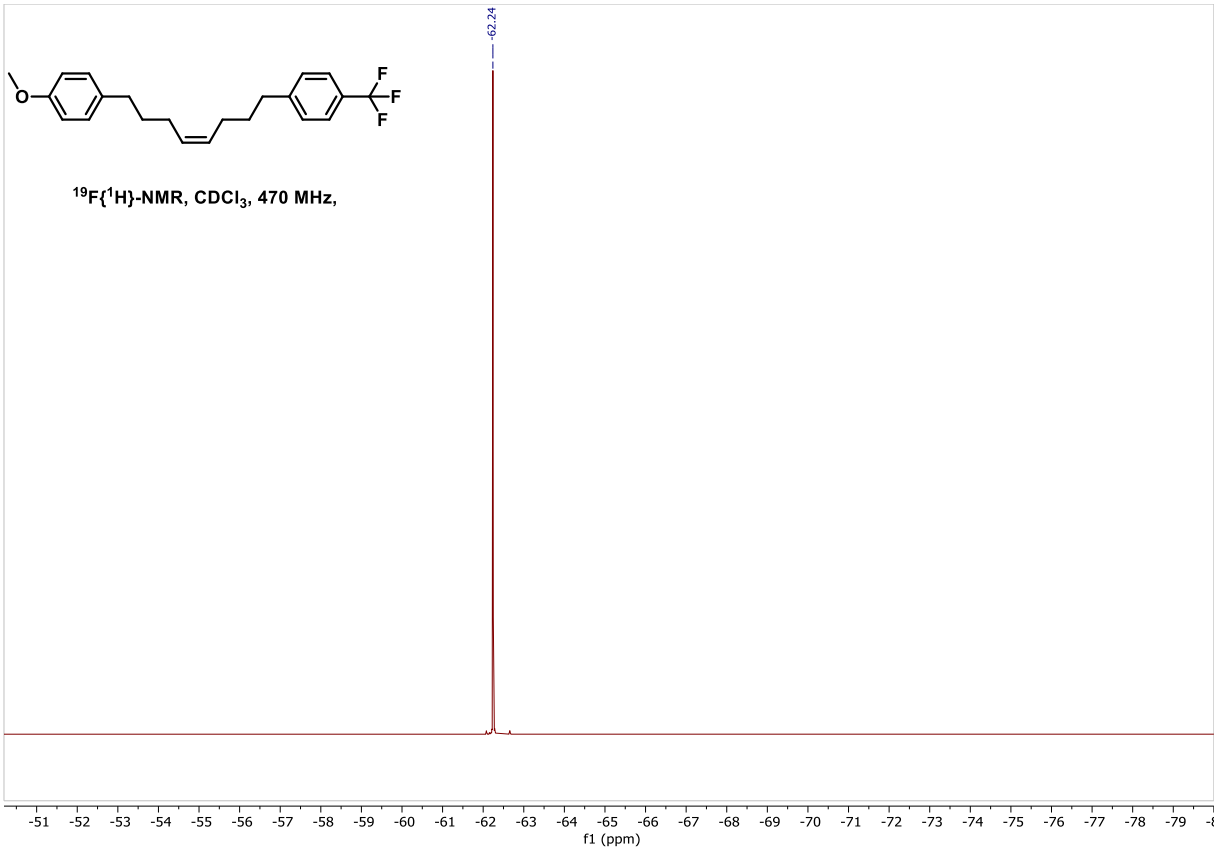


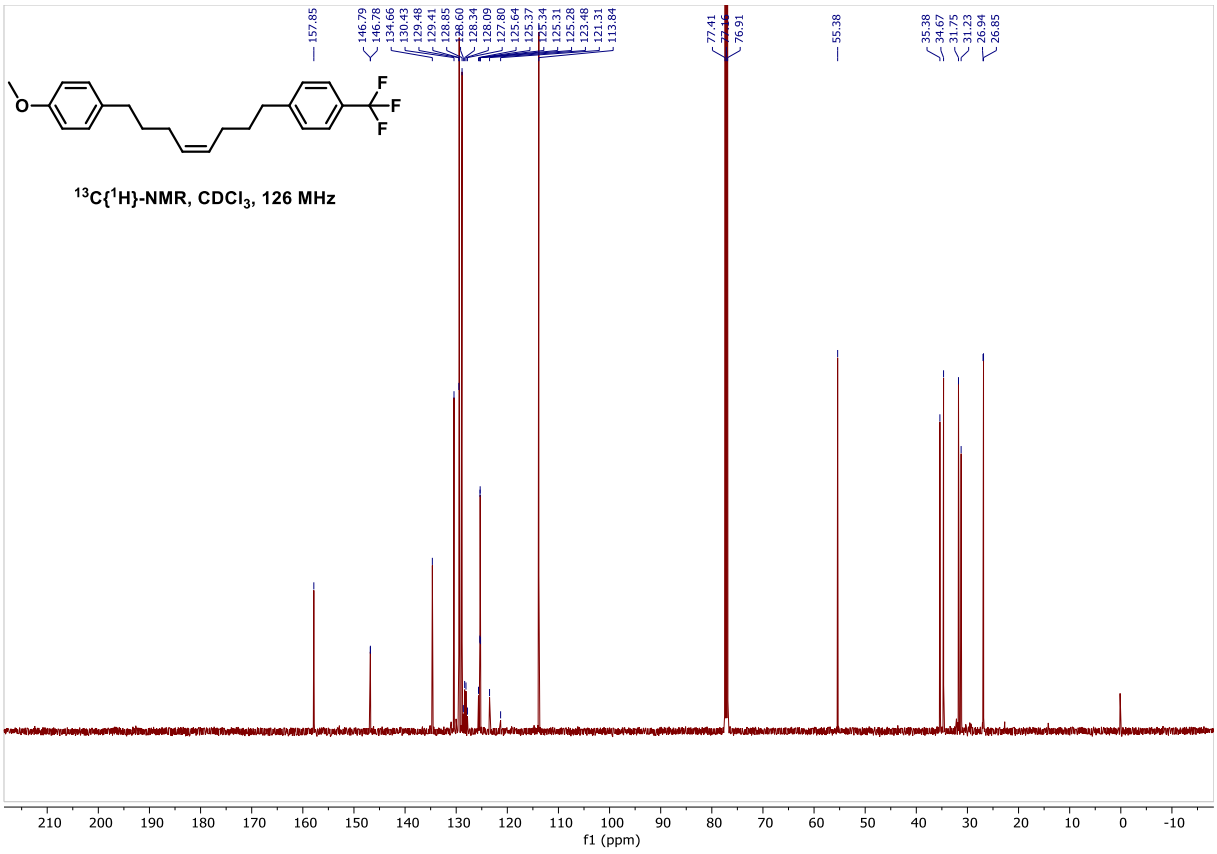

-62.30
F
F
F
O
$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 470 MHz,
-51 -52 -53 -54 -55 -56 -57 -58 -59 -60 -61 -62 -63 -64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79
f1 (ppm)


157.97
146.13
146.11
133.98
129.53
129.19
128.97
128.52
128.26
125.59
125.44
125.41
125.38
125.35
123.43
113.91
80.90
79.91
77.41
77.16
76.91
55.40
34.74
34.07
31.09
30.53
18.32
18.31
F
F
F
O
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

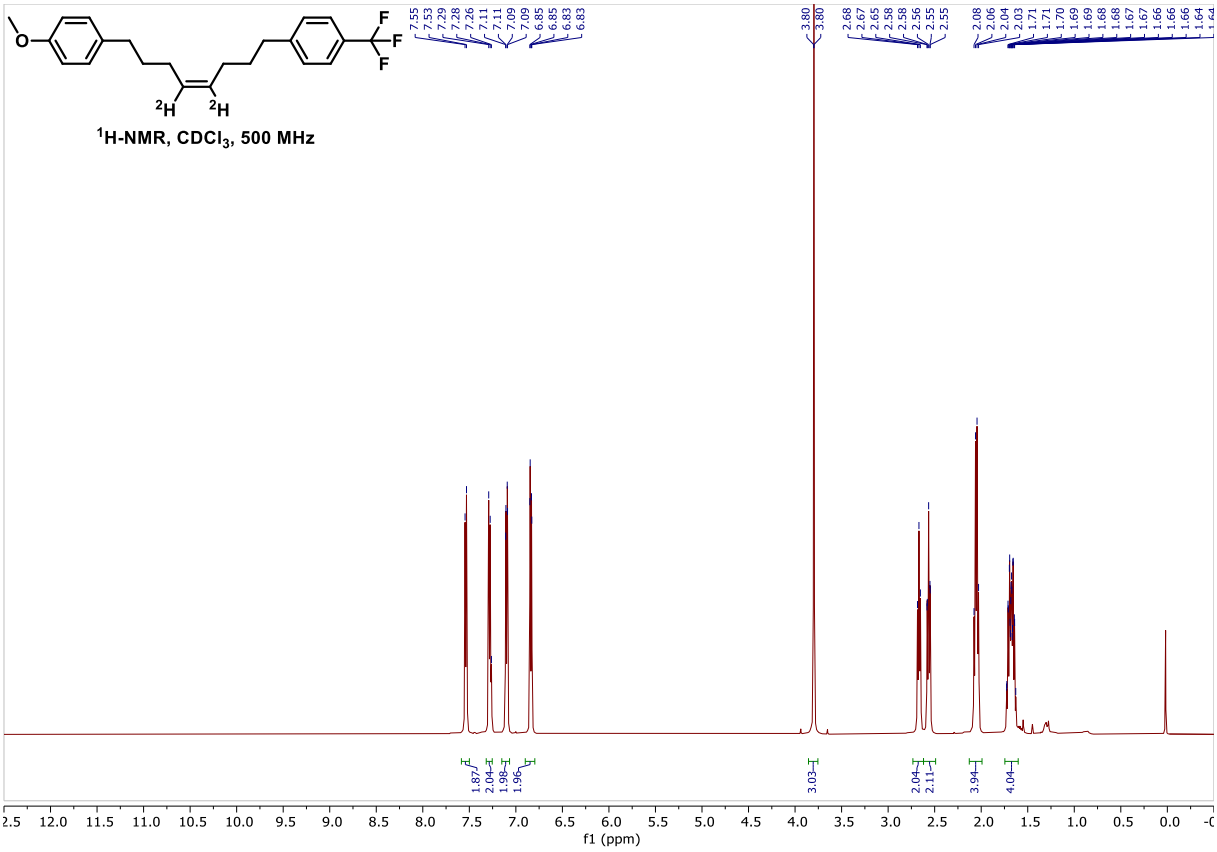
(*Z*)-1-Methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl)benzene (**3.1r**)

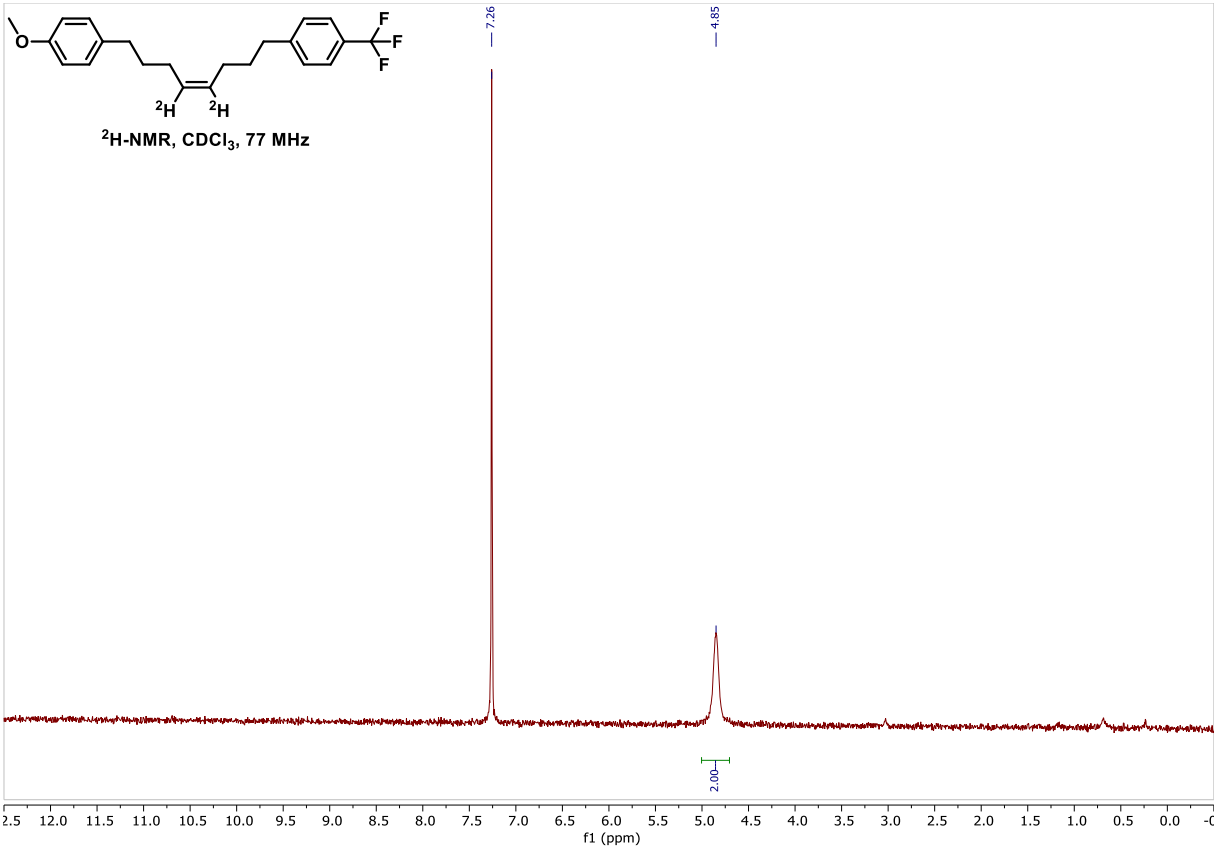




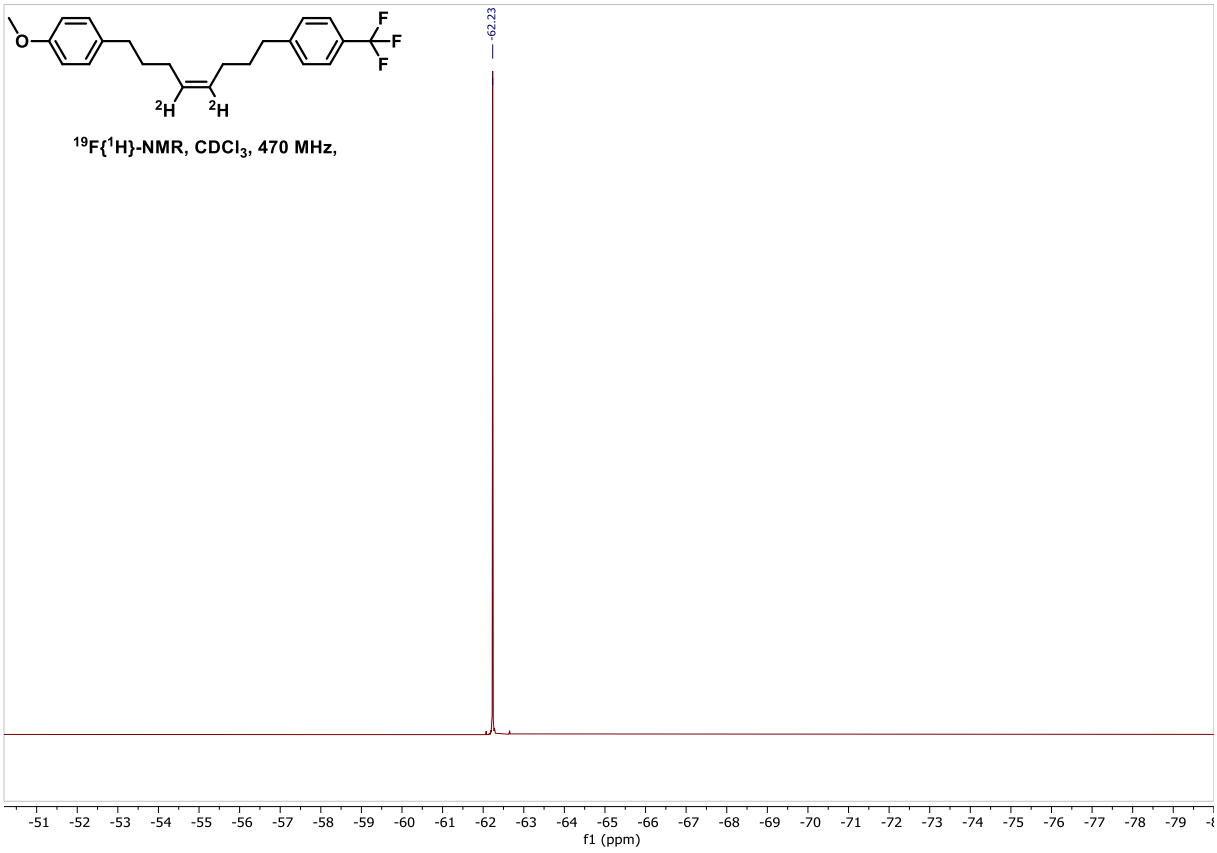


(*Z*)-1-Methoxy-4-(8-(4-(trifluoromethyl)phenyl)oct-4-en-1-yl-4,5-d2)benzene (**3.1r-*D*$_2$**)

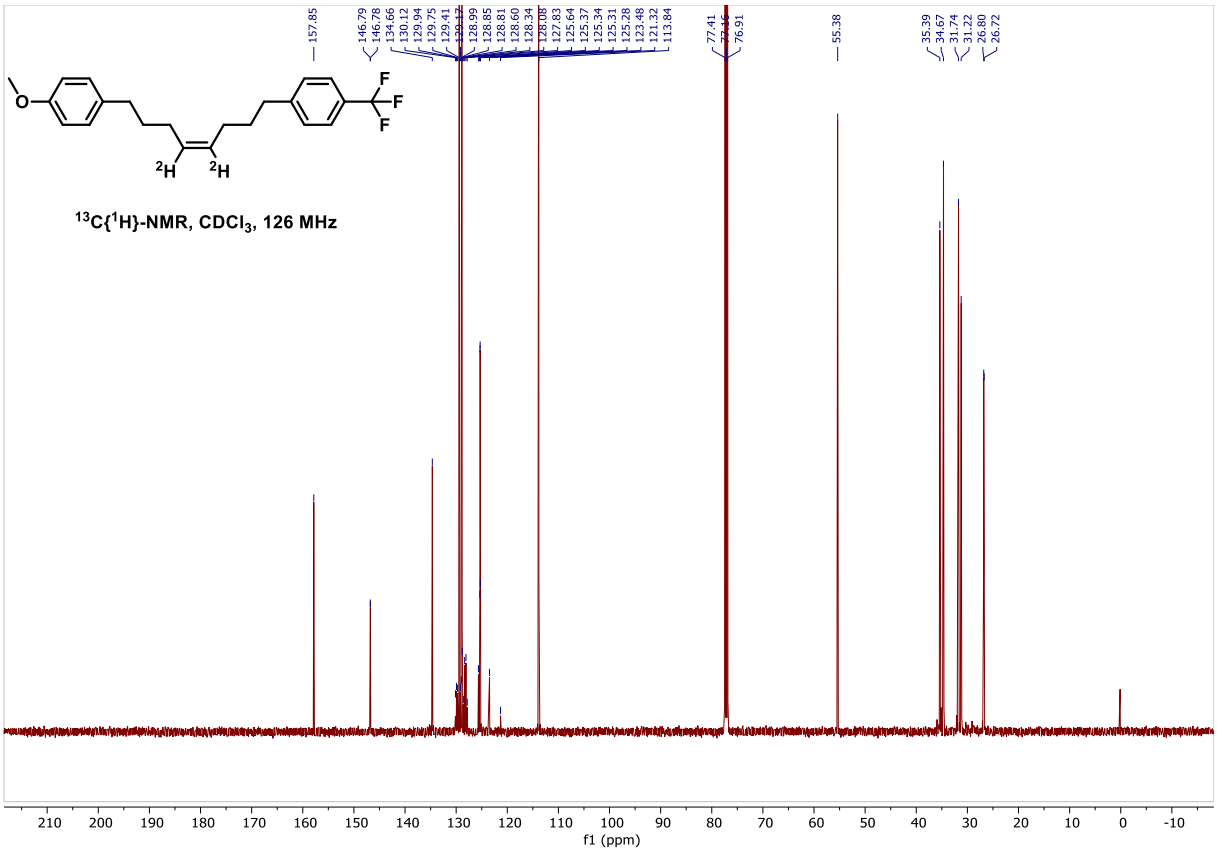




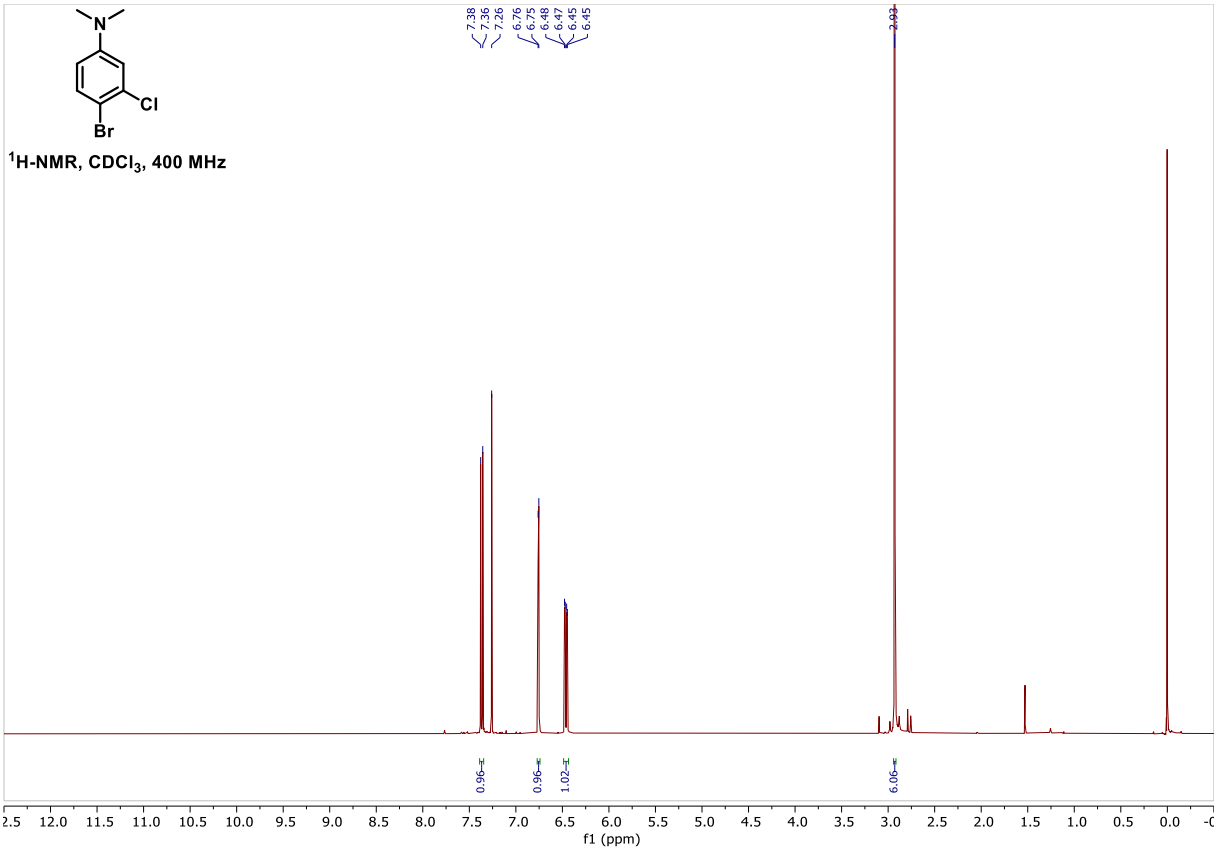
^{2}H-NMR, $CDCl_3$, 77 MHz

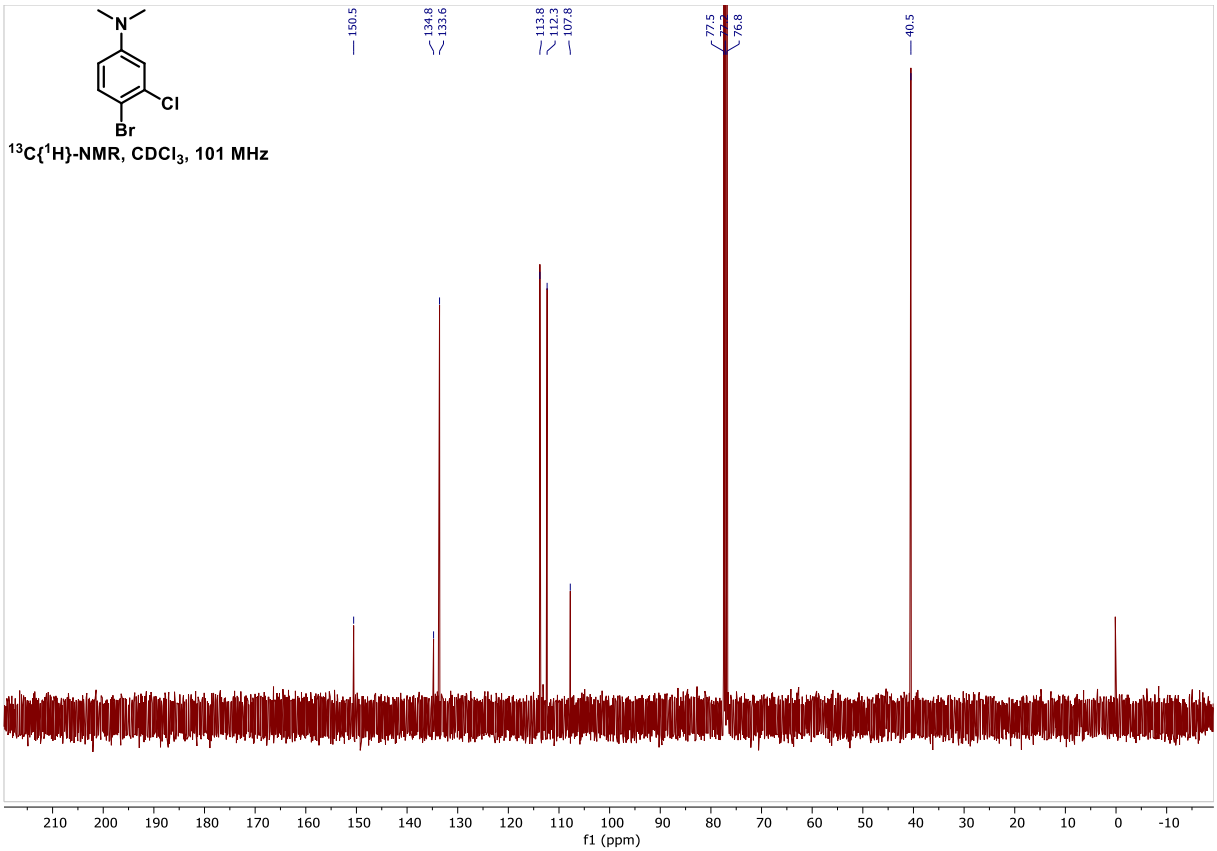


$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 470 MHz,

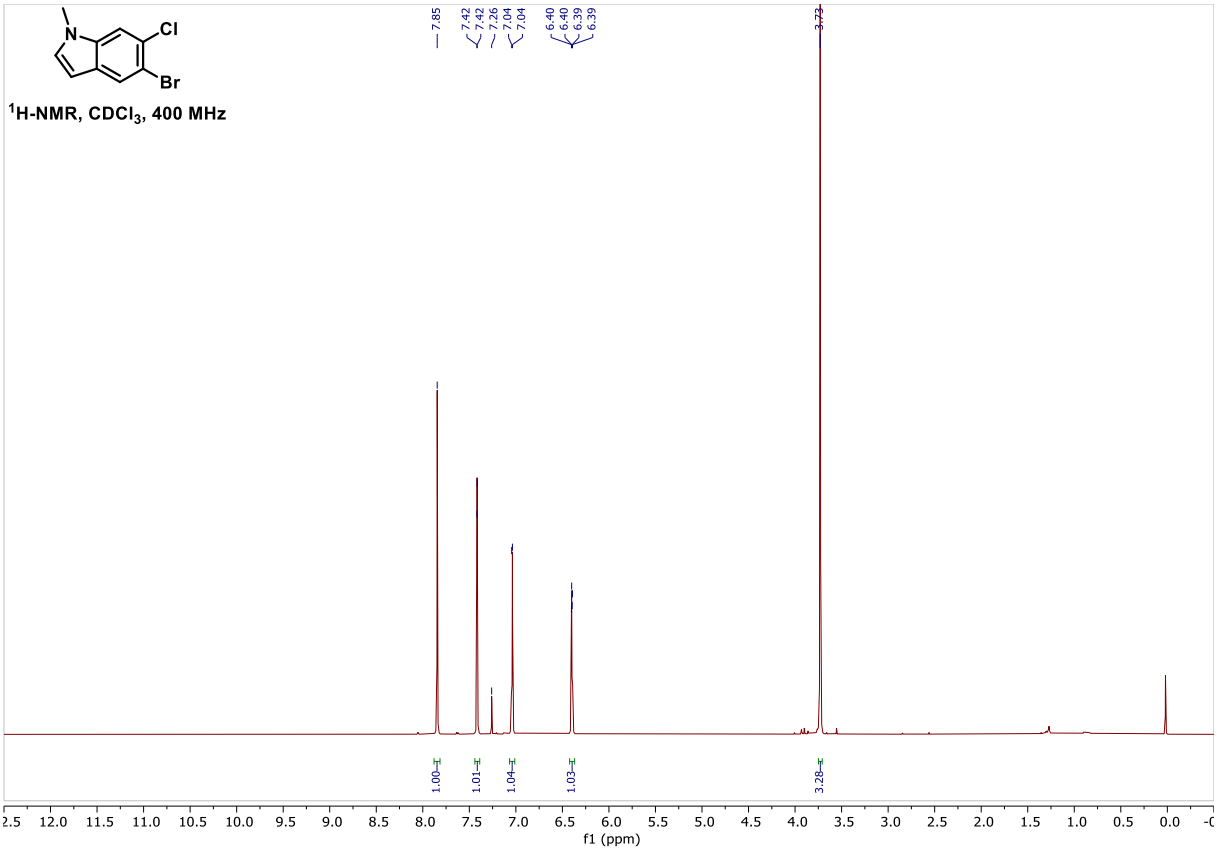


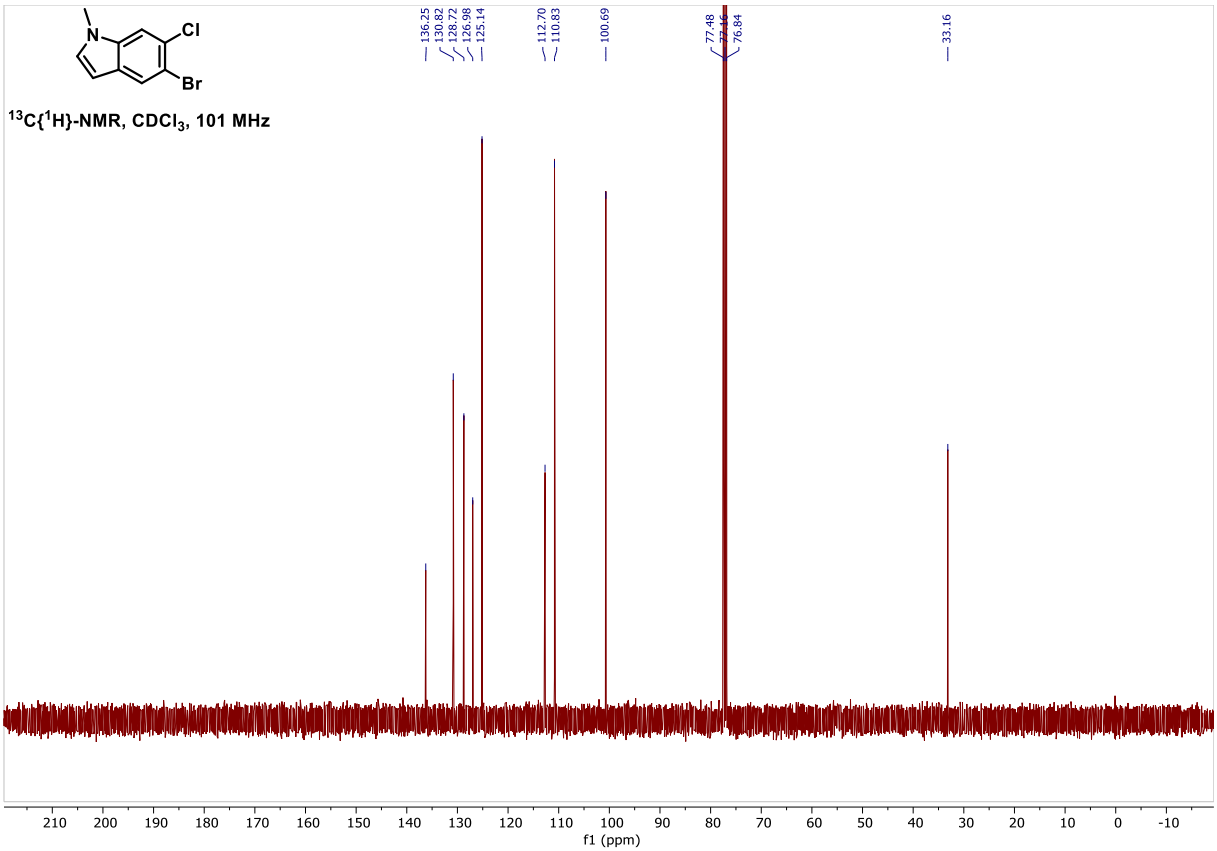
4-Bromo-3-chloro-N,N-dimethylaniline (**S1a**)



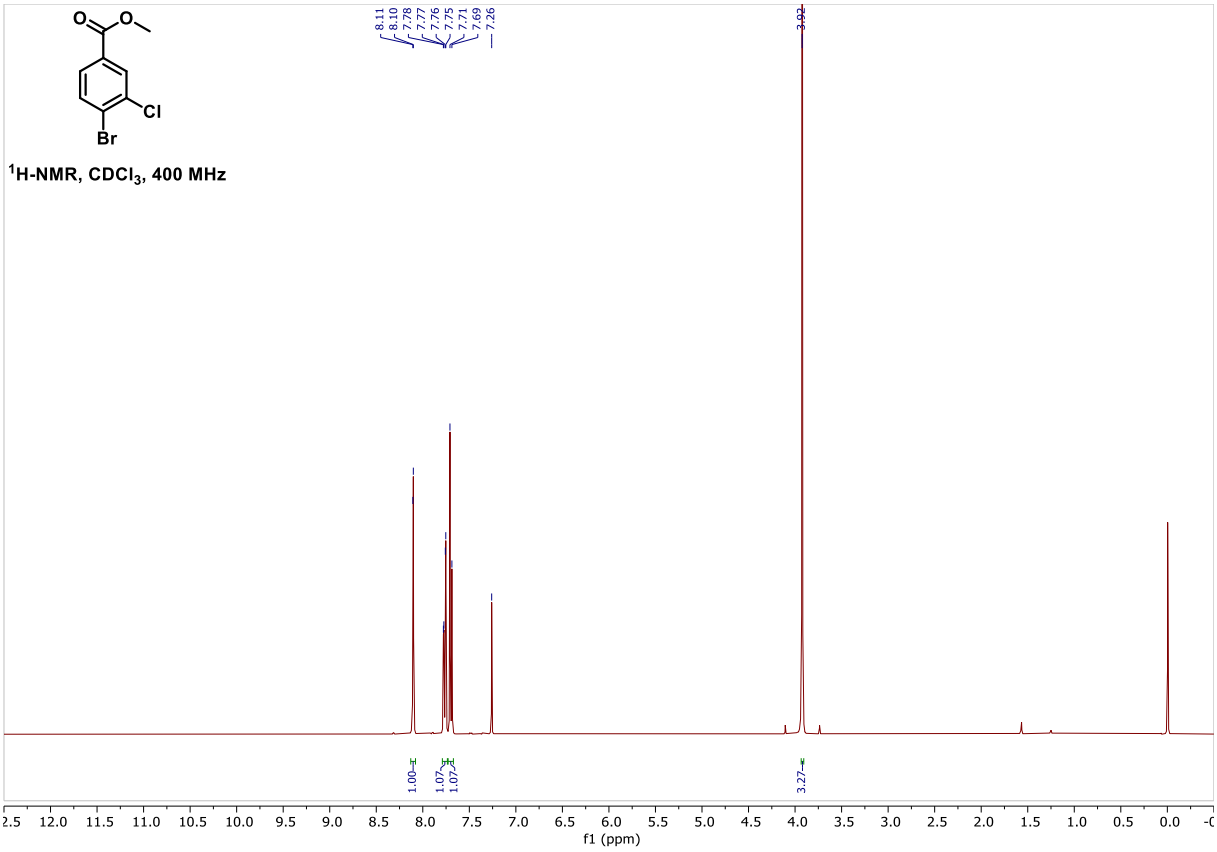


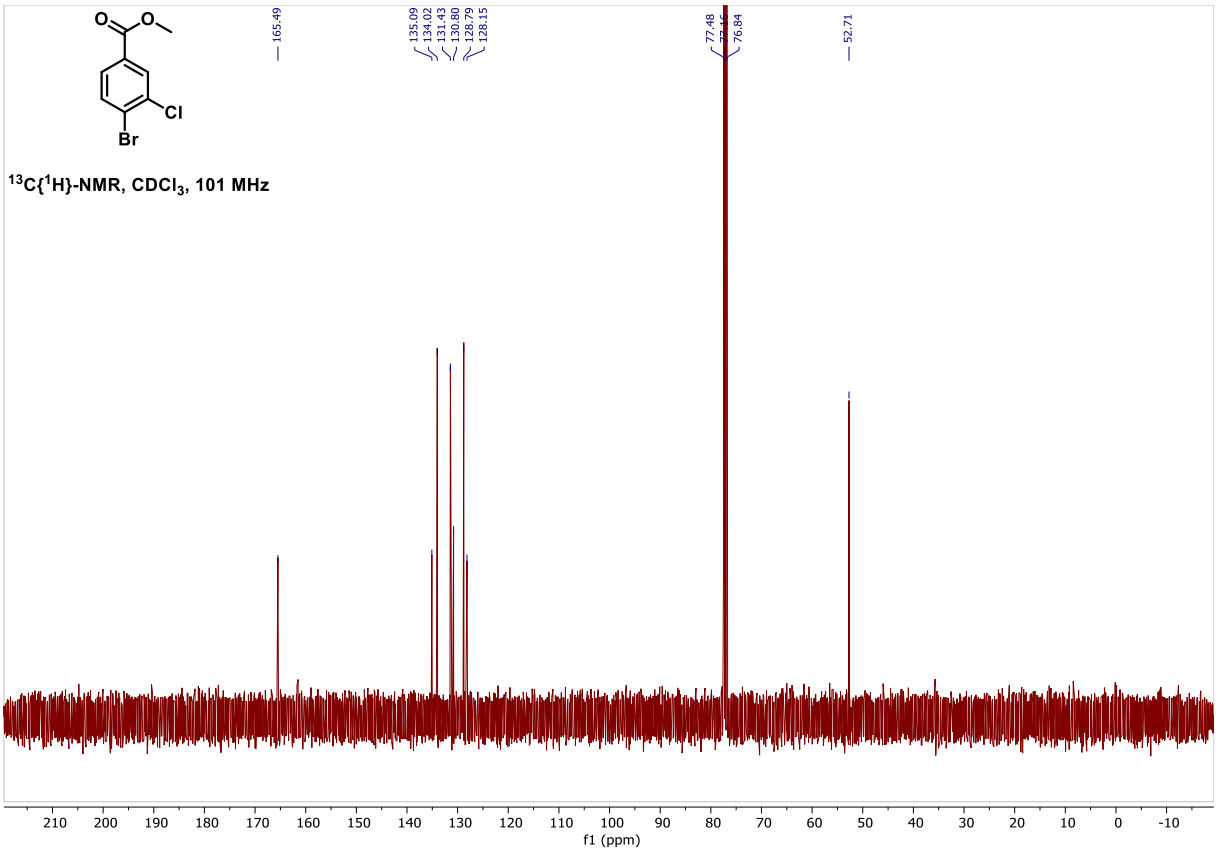
5-Bromo-6-chloro-1-methyl-1H-indole (**S1b**)



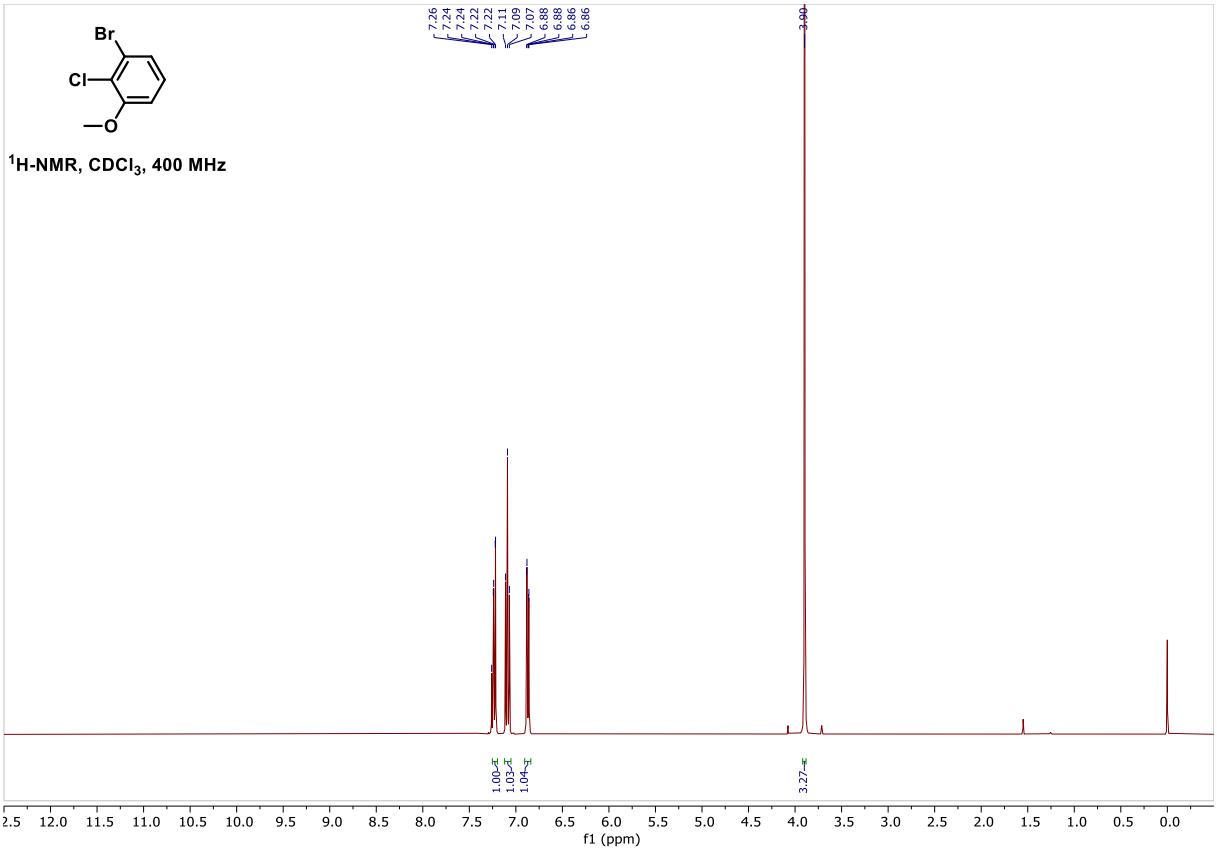


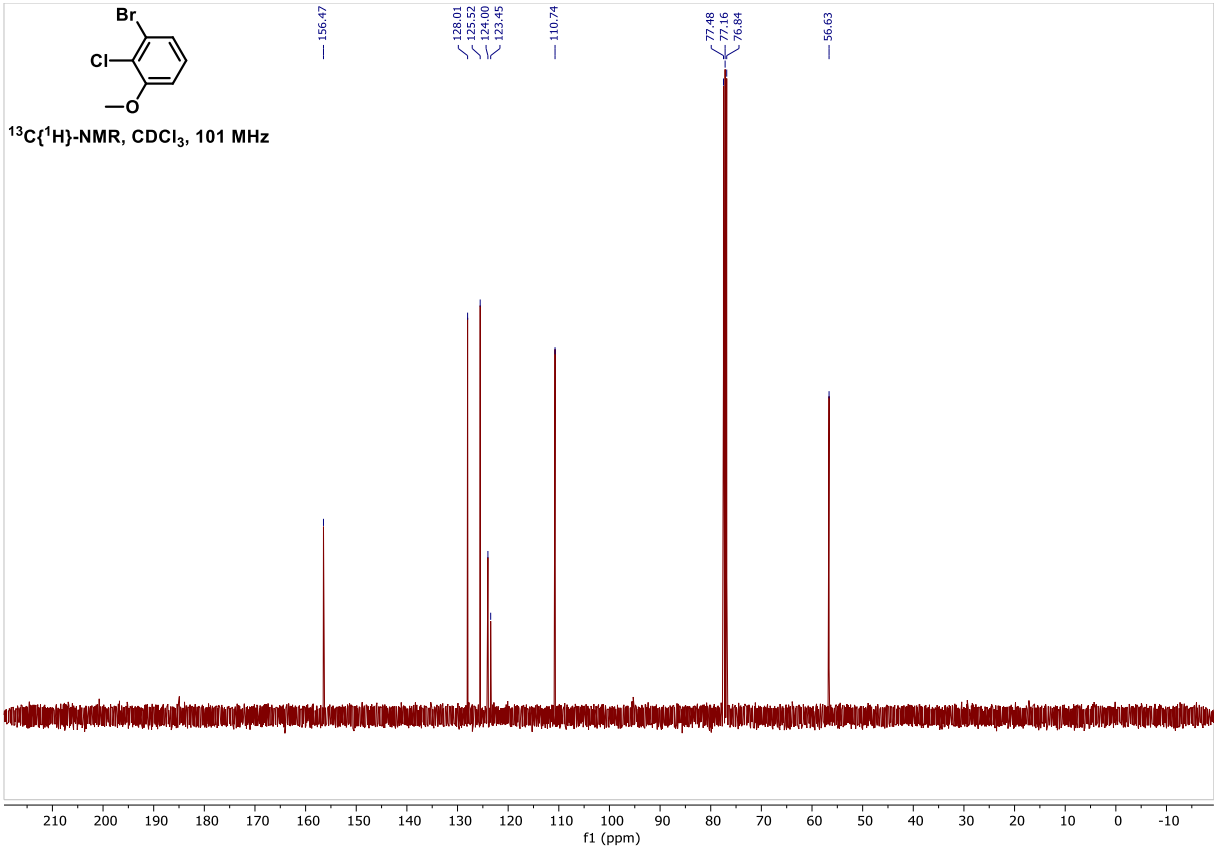
Methyl 4-bromo-3-chlorobenzoate (**S1c**)



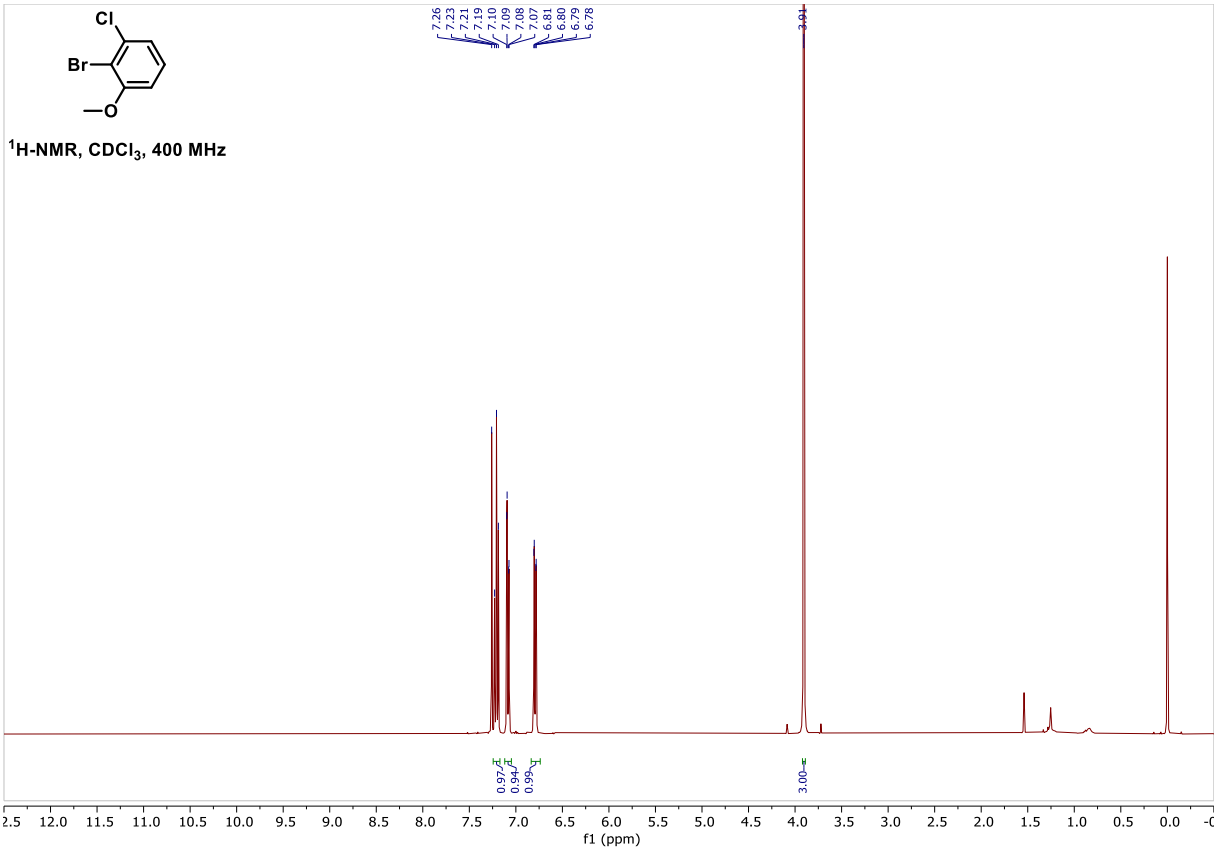


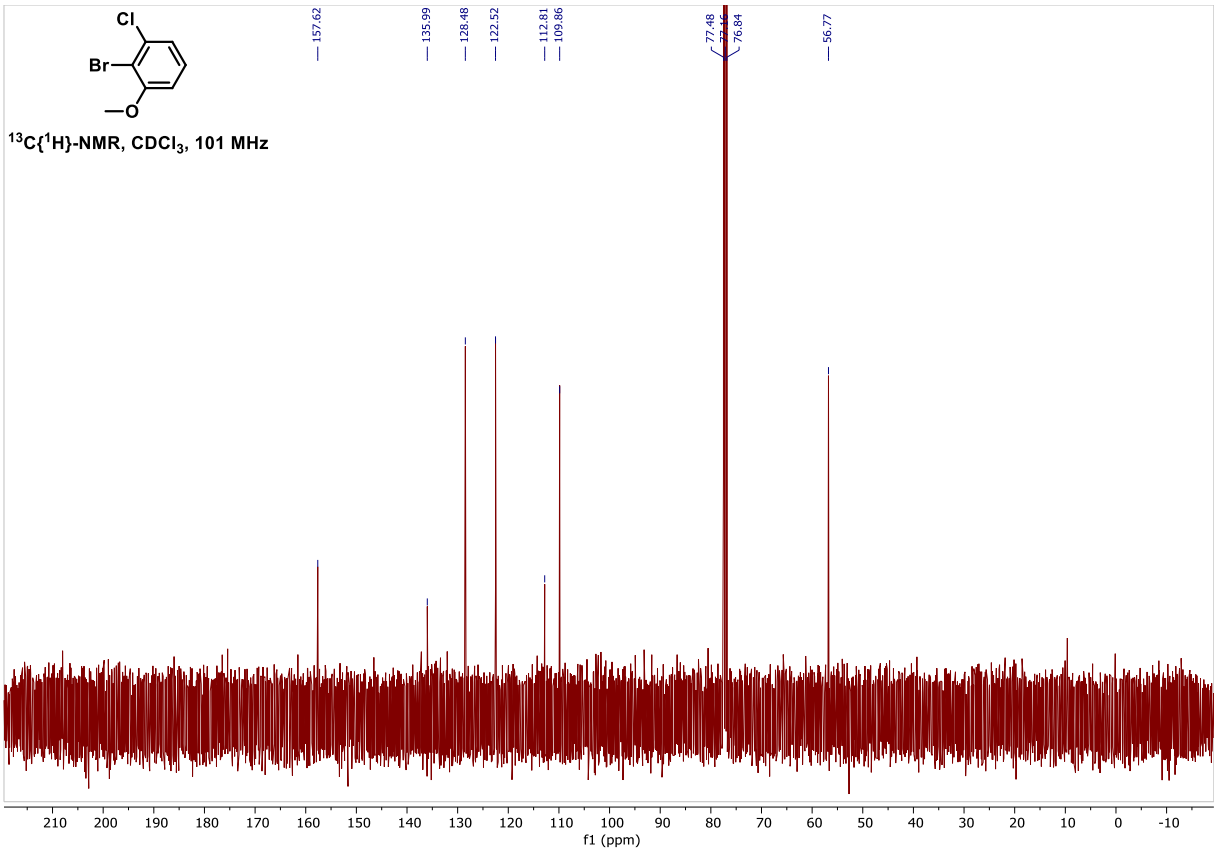
1-Bromo-2-chloro-3-methoxybenzene (**S1d**)



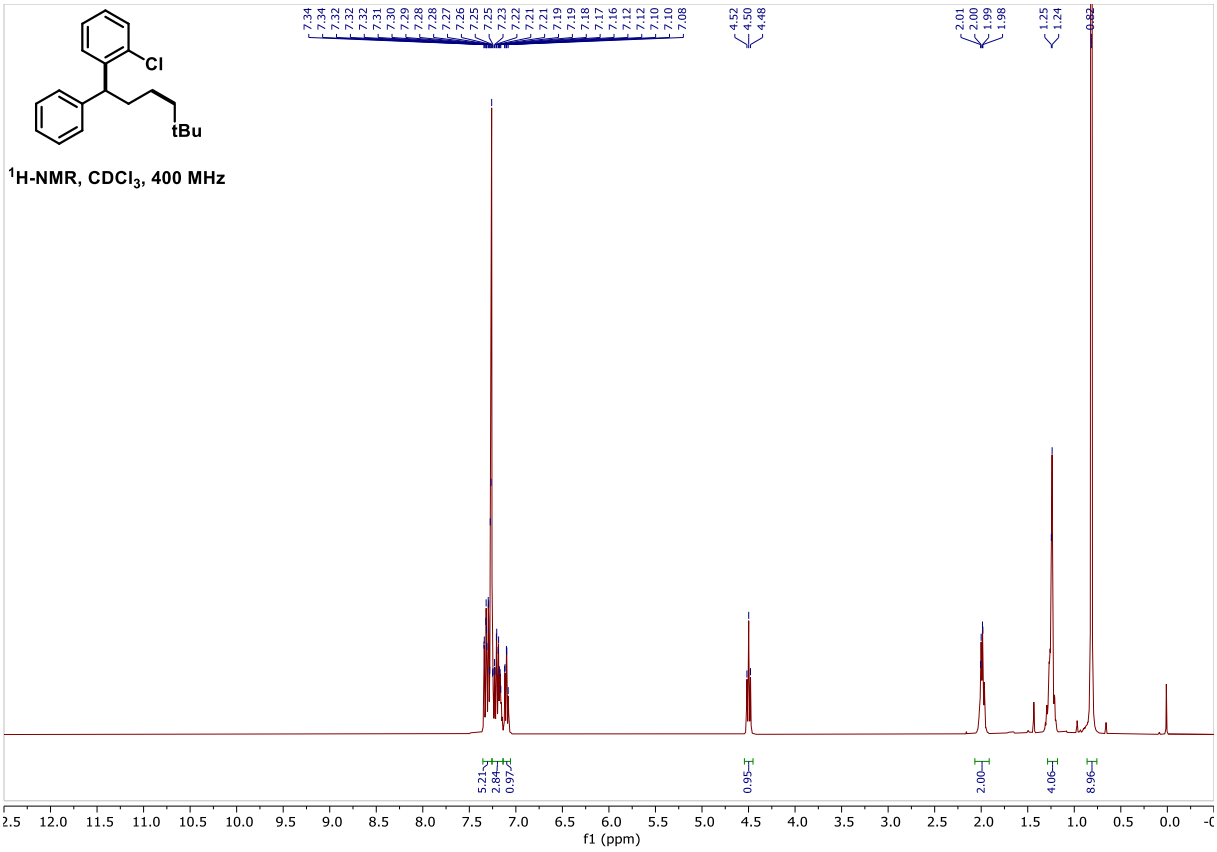


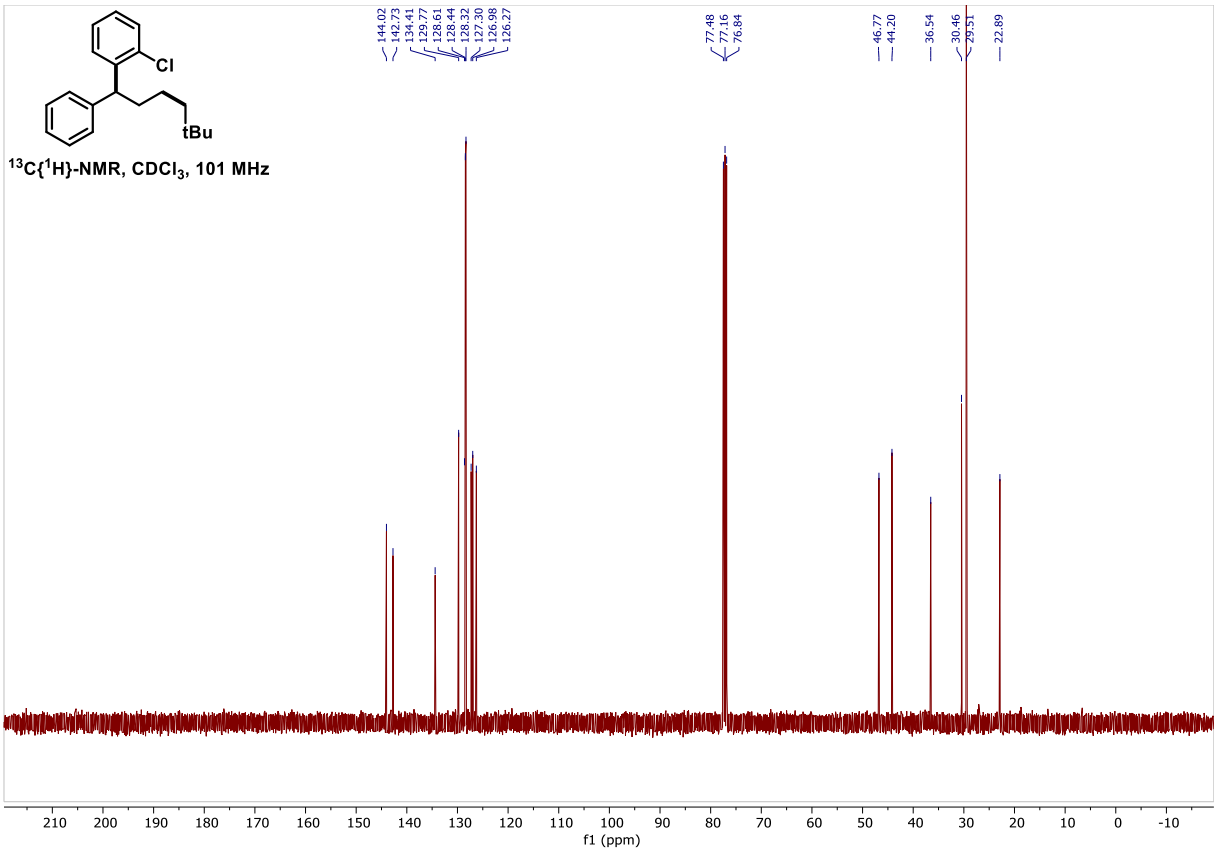
2-Bromo-1-chloro-3-methoxybenzene (**S1e**)



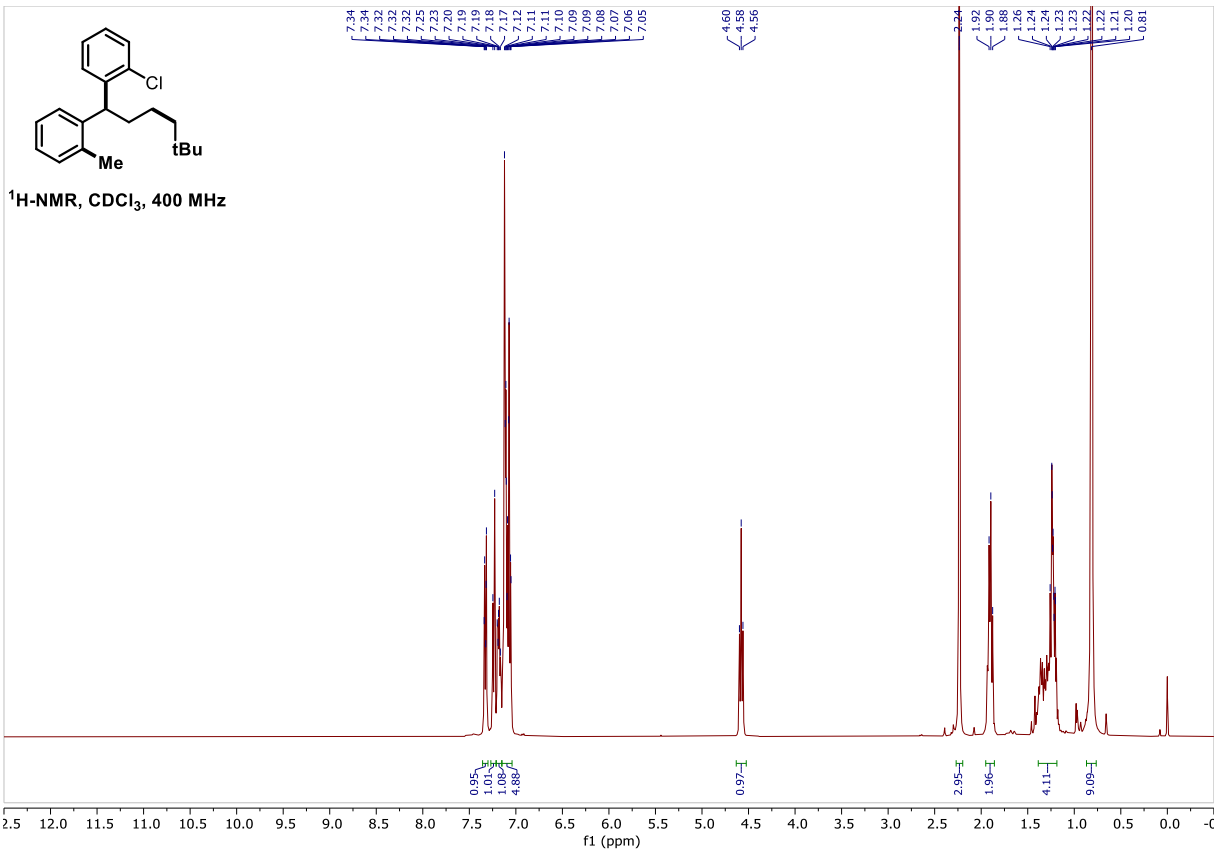


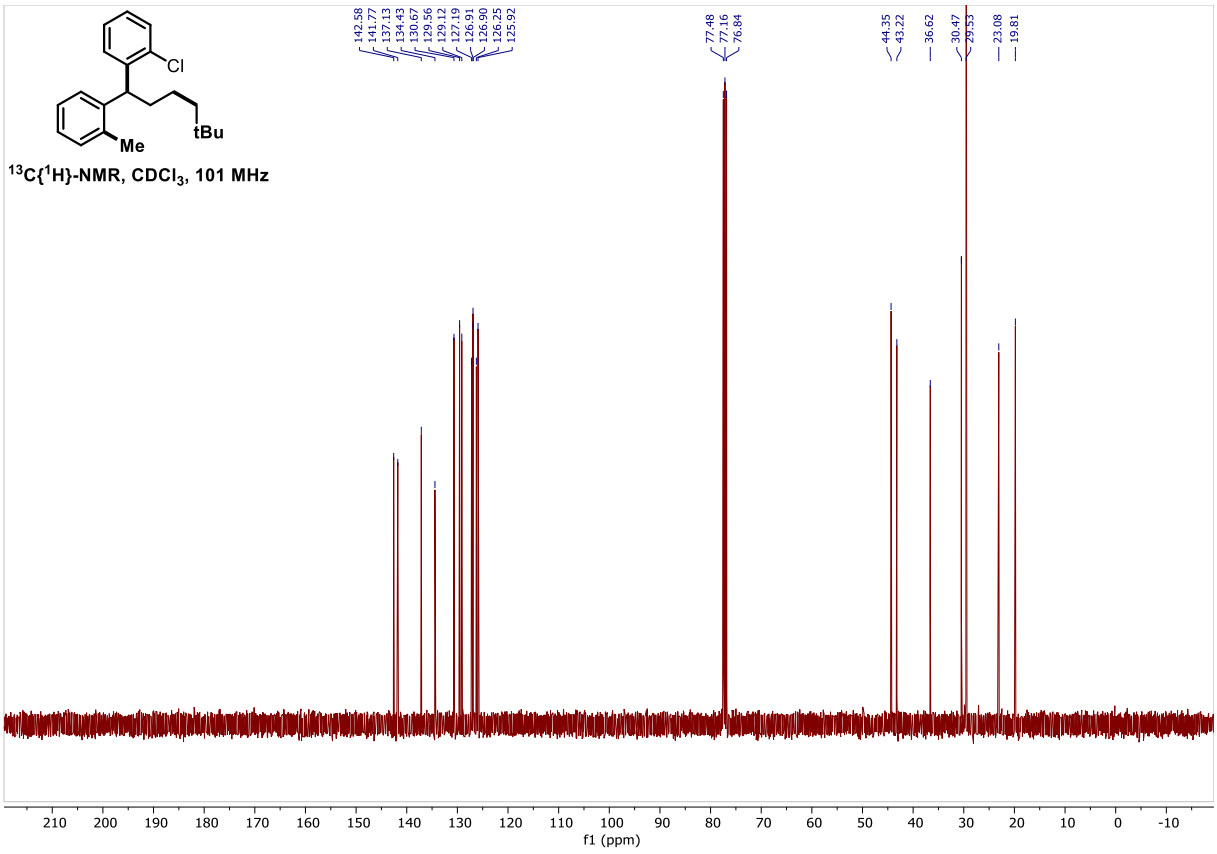
1-Chloro-2-(5,5-dimethyl-1-phenylhexyl)benzene (**3.3a**)



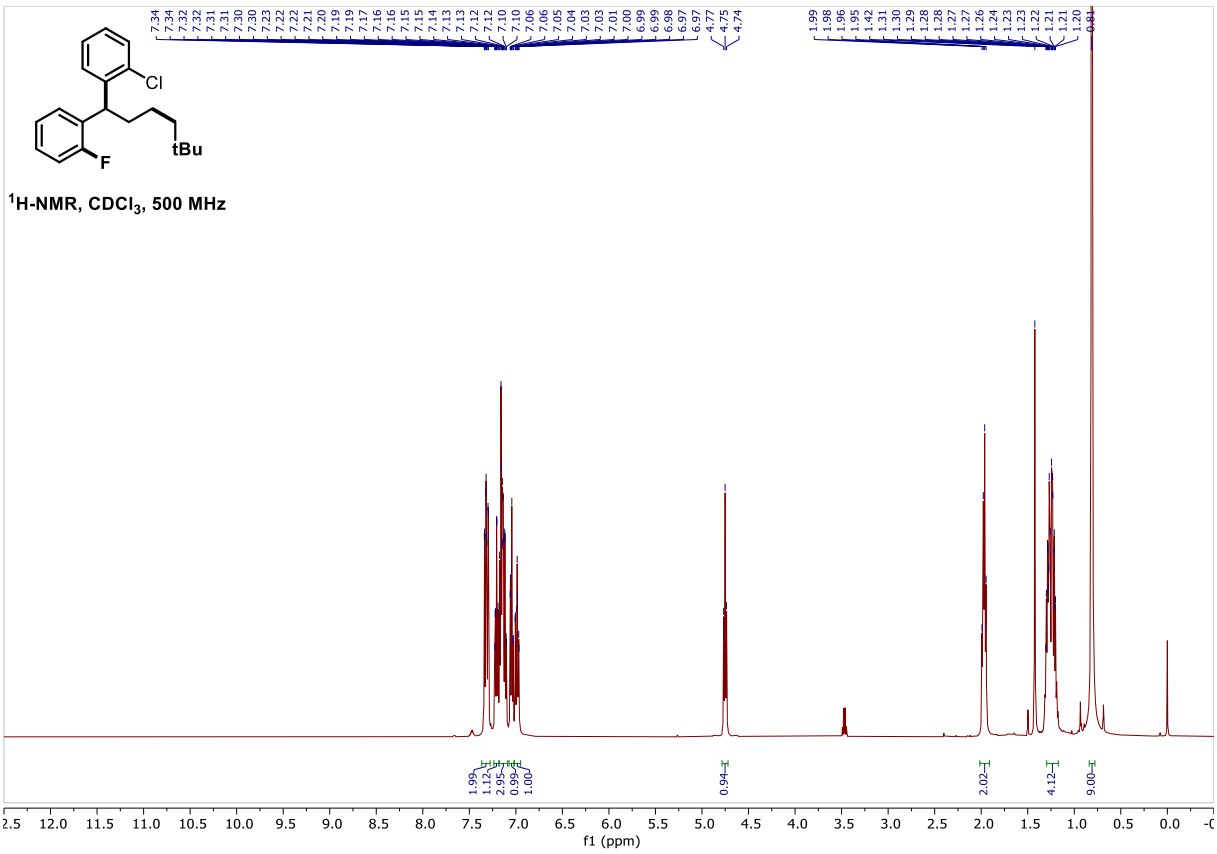


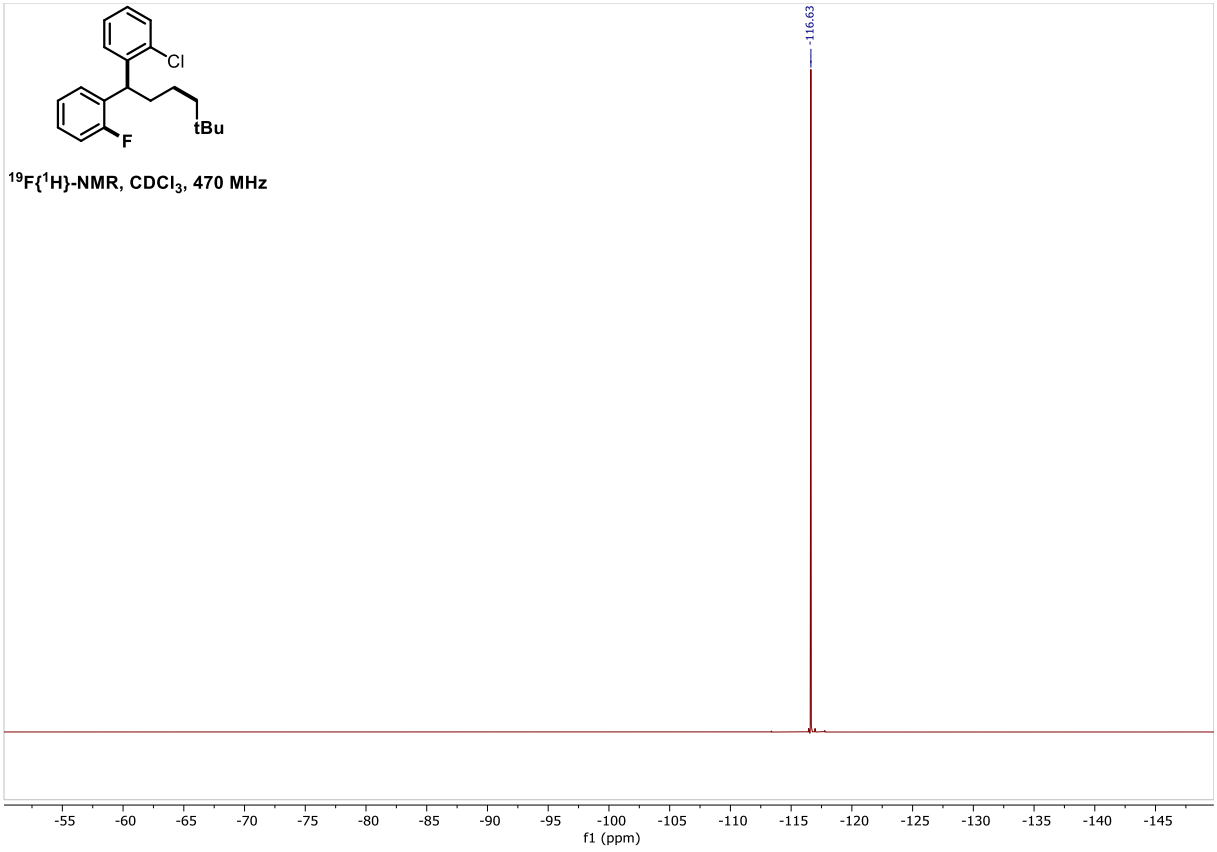
1-Chloro-2-(5,5-dimethyl-1-(o-tolyl)hexyl)benzene (**3.3c**)



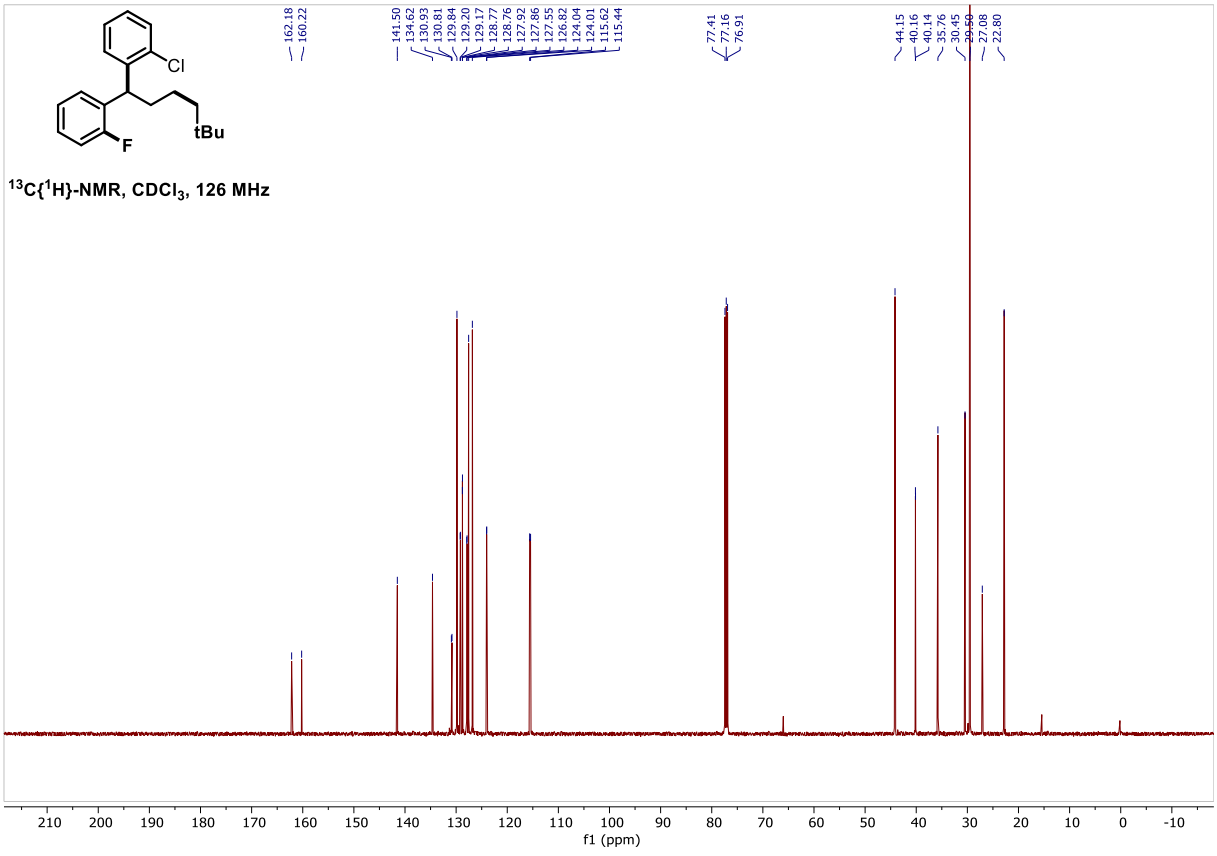


1-Chloro-2-(1-(2-fluorophenyl)-5,5-dimethylhexyl)benzene (**3.3d**)



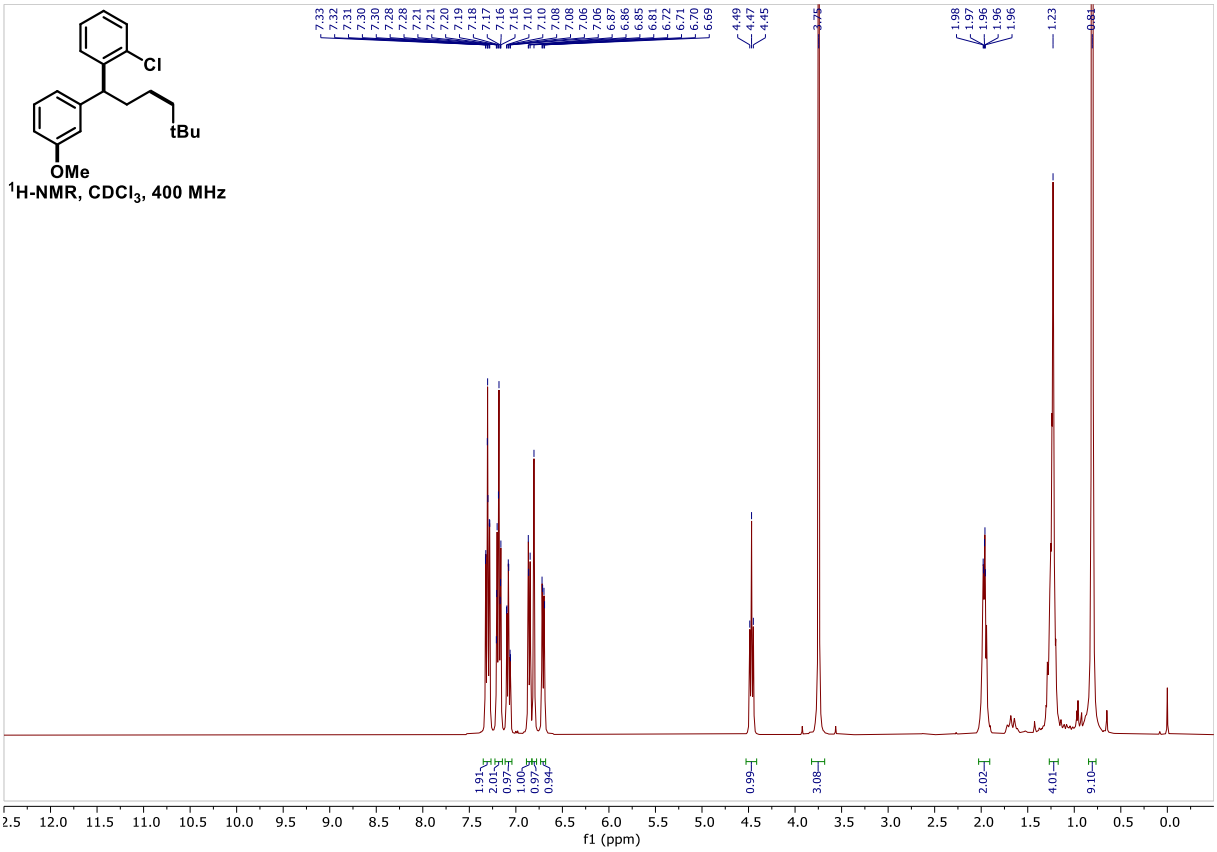


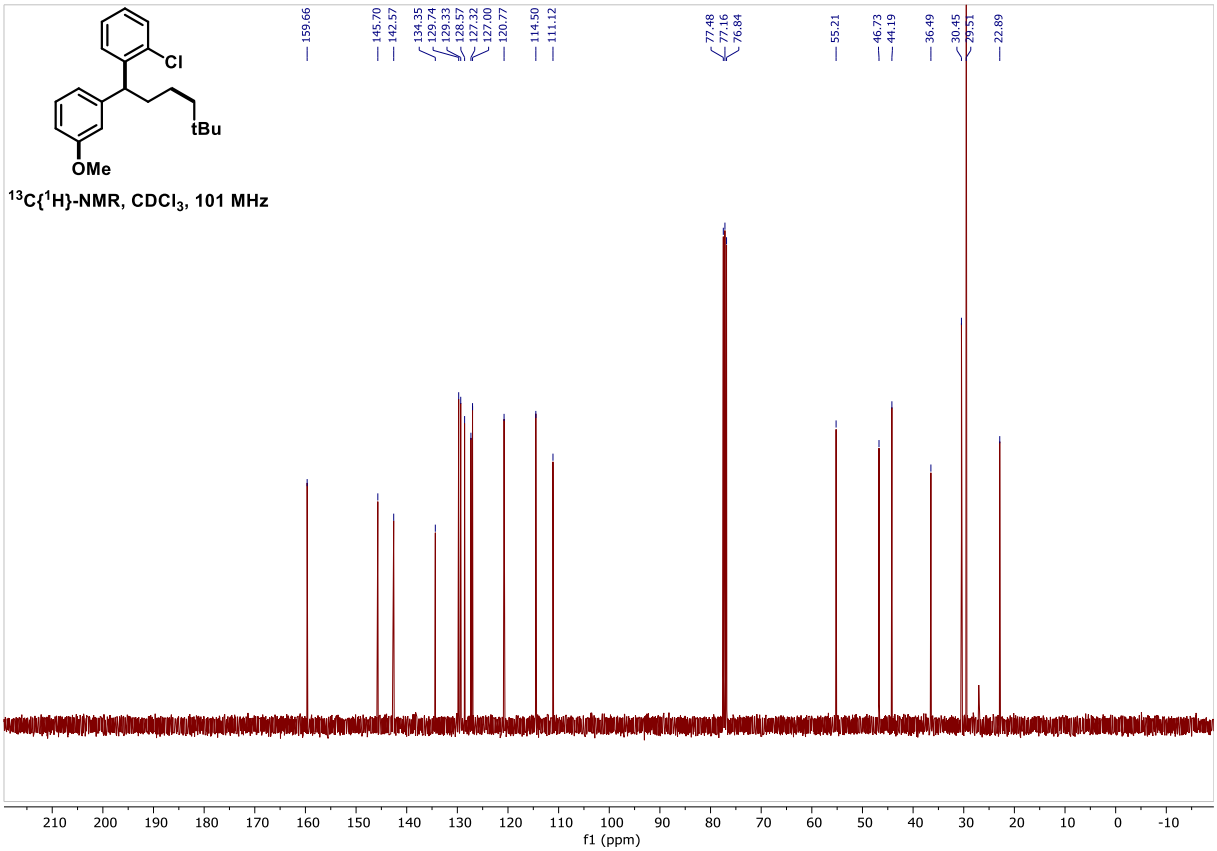
$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 470 MHz



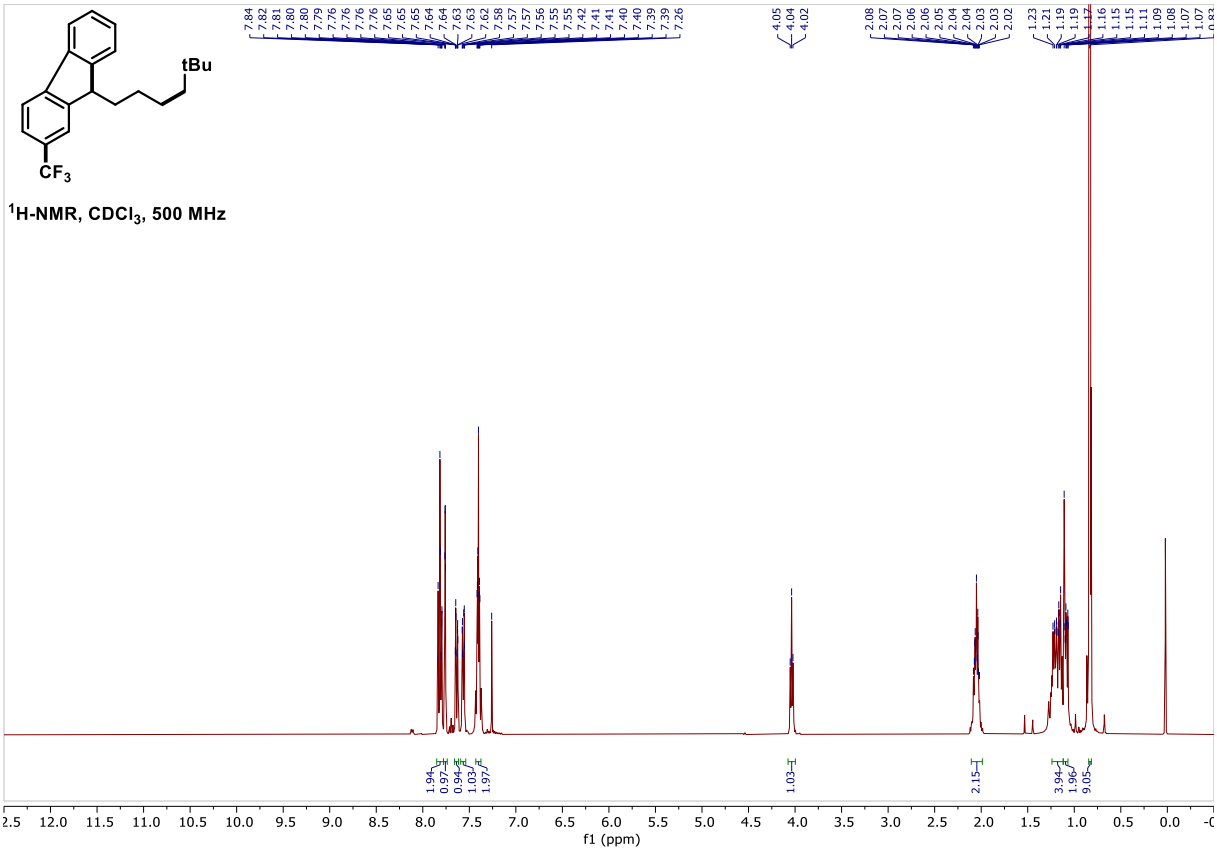
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 126 MHz

1-Chloro-2-(1-(3-methoxyphenyl)-5,5-dimethylhexyl)benzene (**3.3e**)

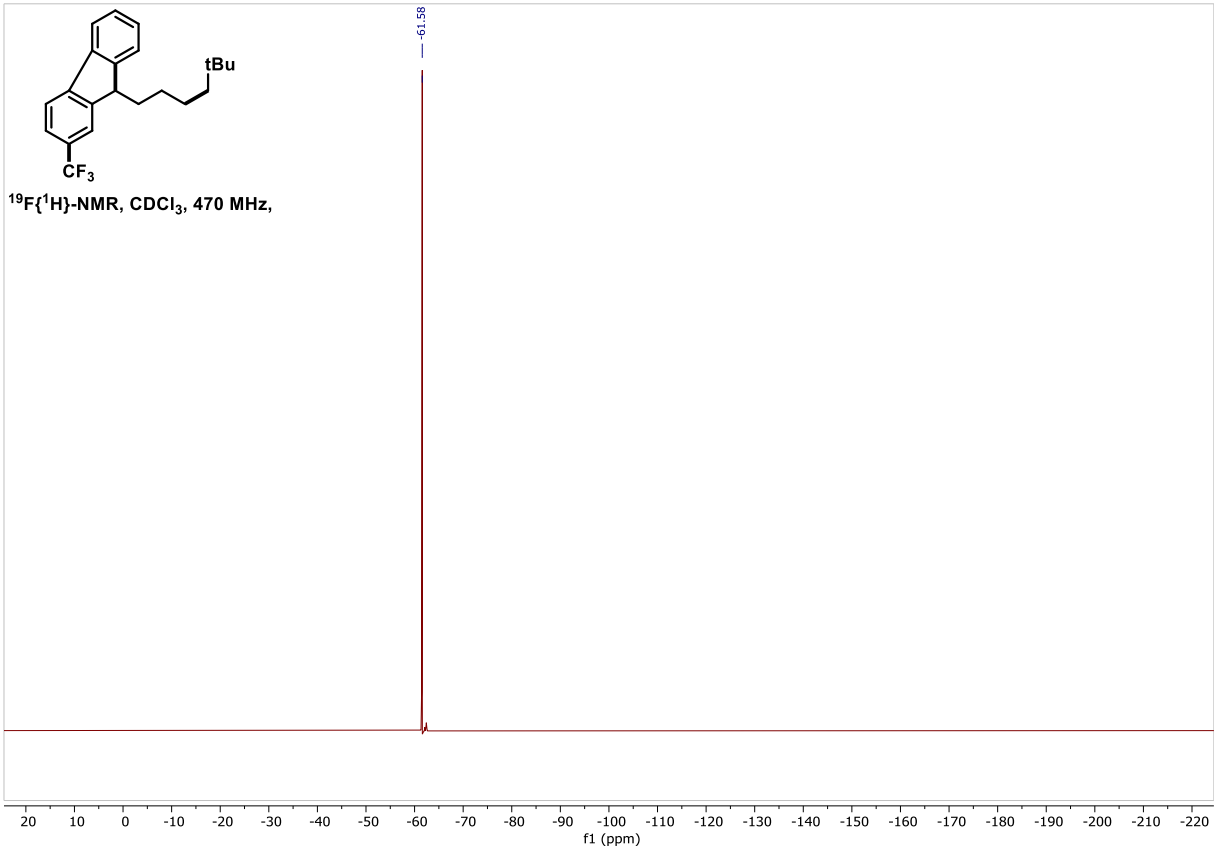




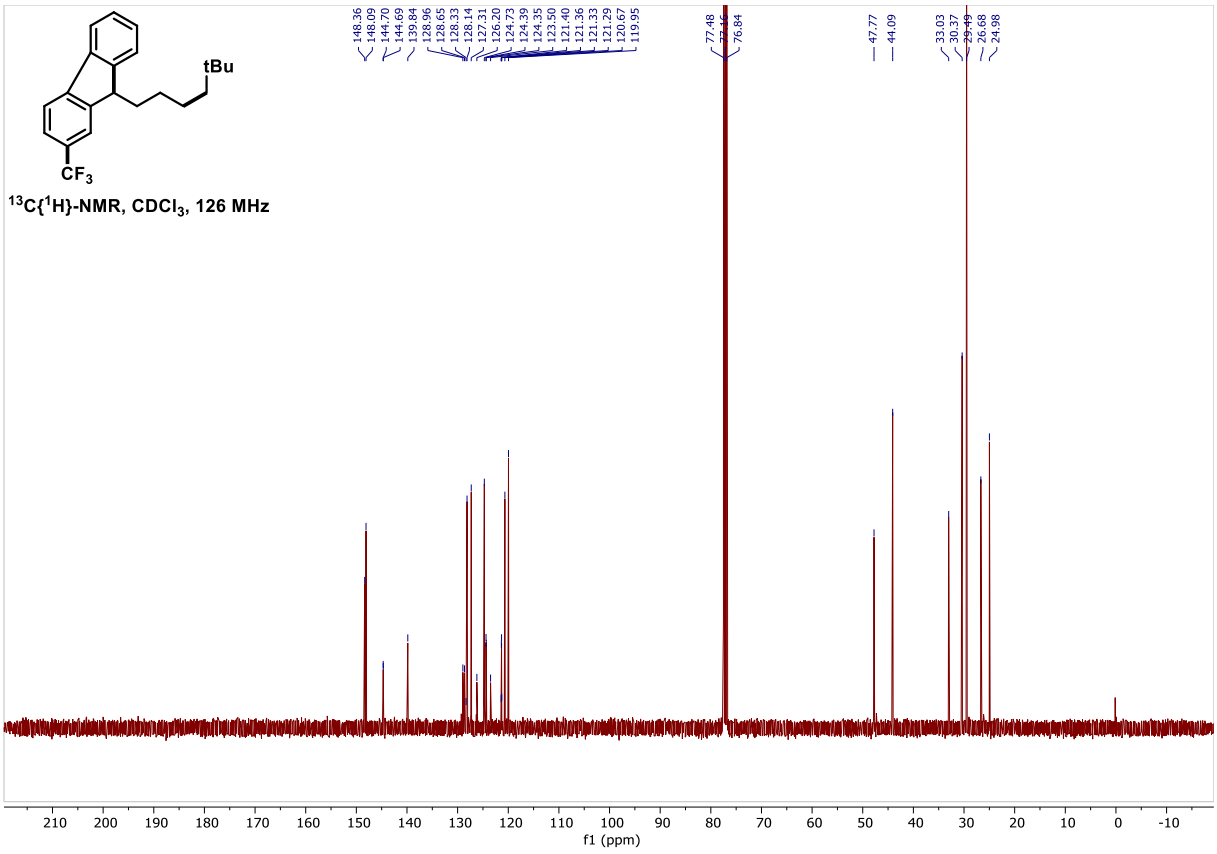
9-(5,5-Dimethylhexyl)-2-(trifluoromethyl)-9H-fluorene (**3.25a**)



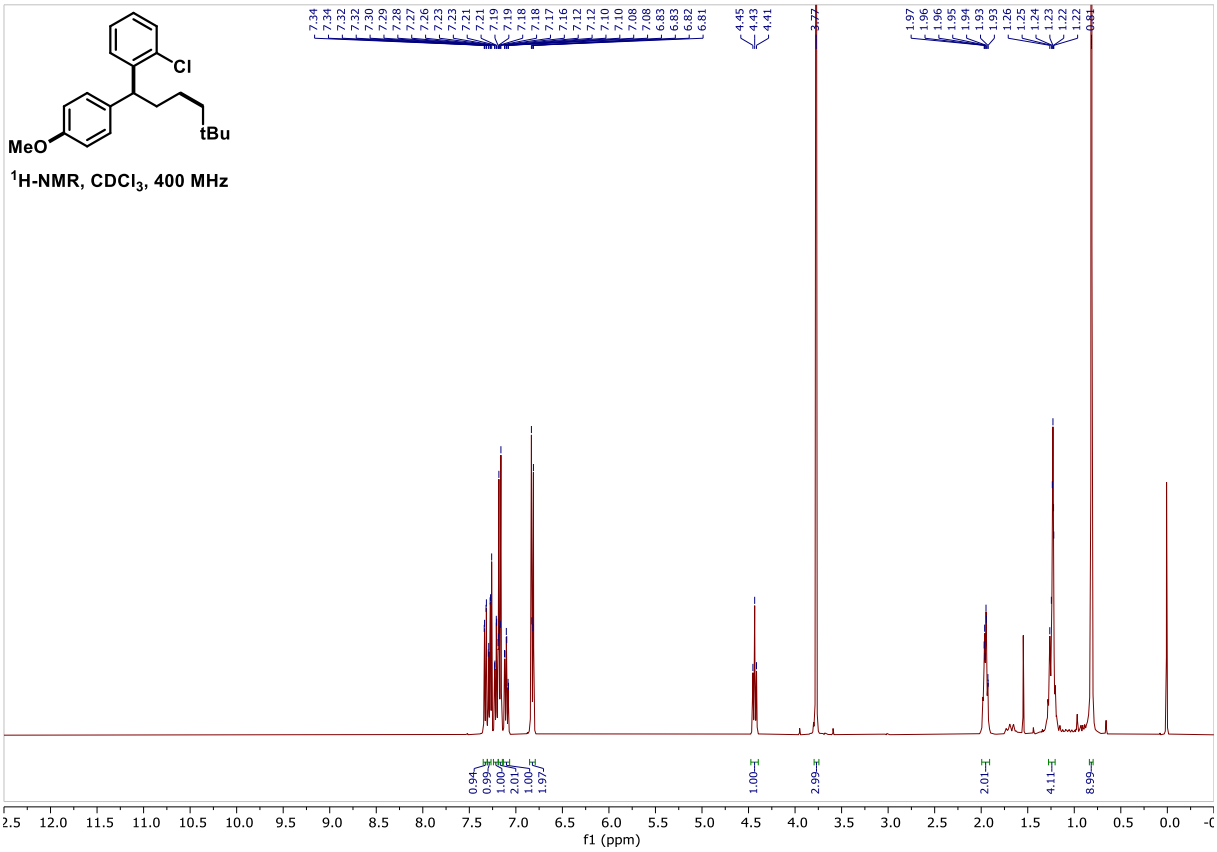
^{1}H-NMR, $CDCl_3$, 500 MHz

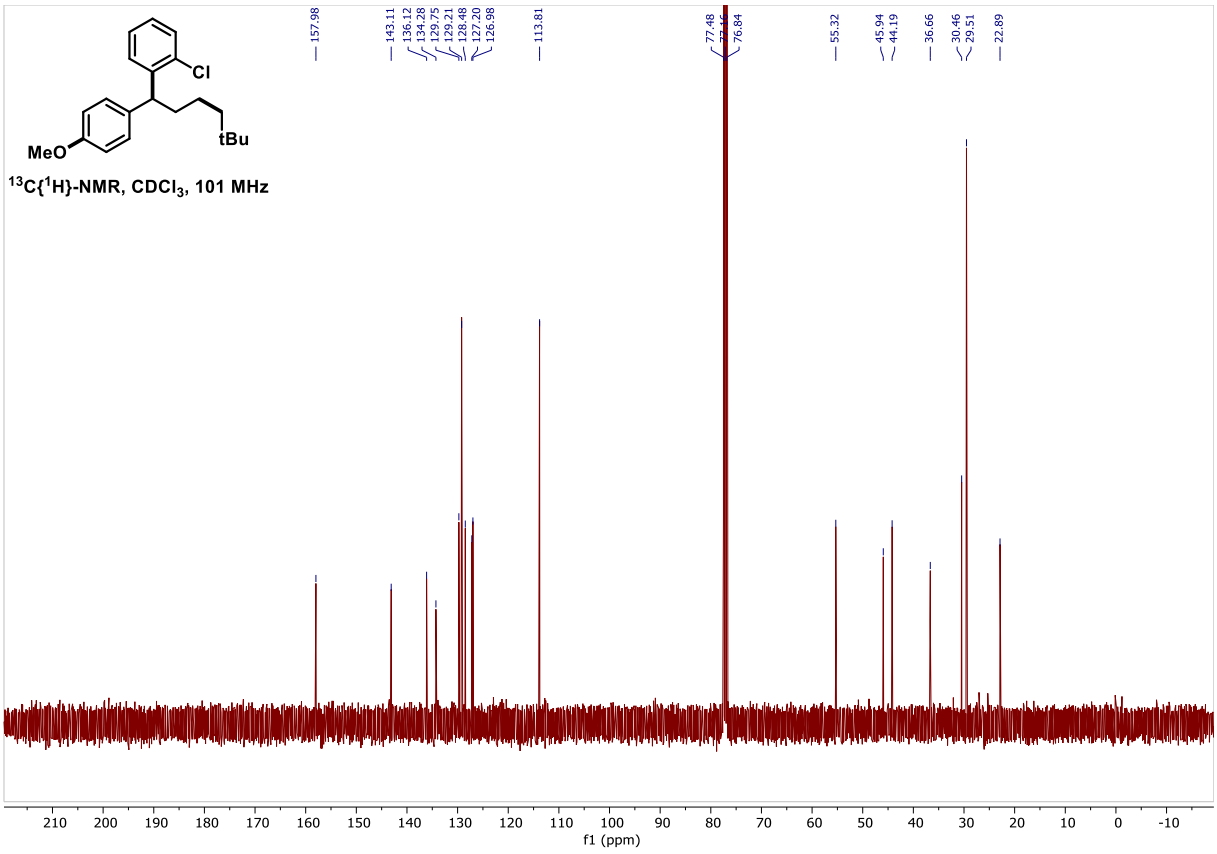


^{19}F{^{1}H}-NMR, $CDCl_3$, 470 MHz,

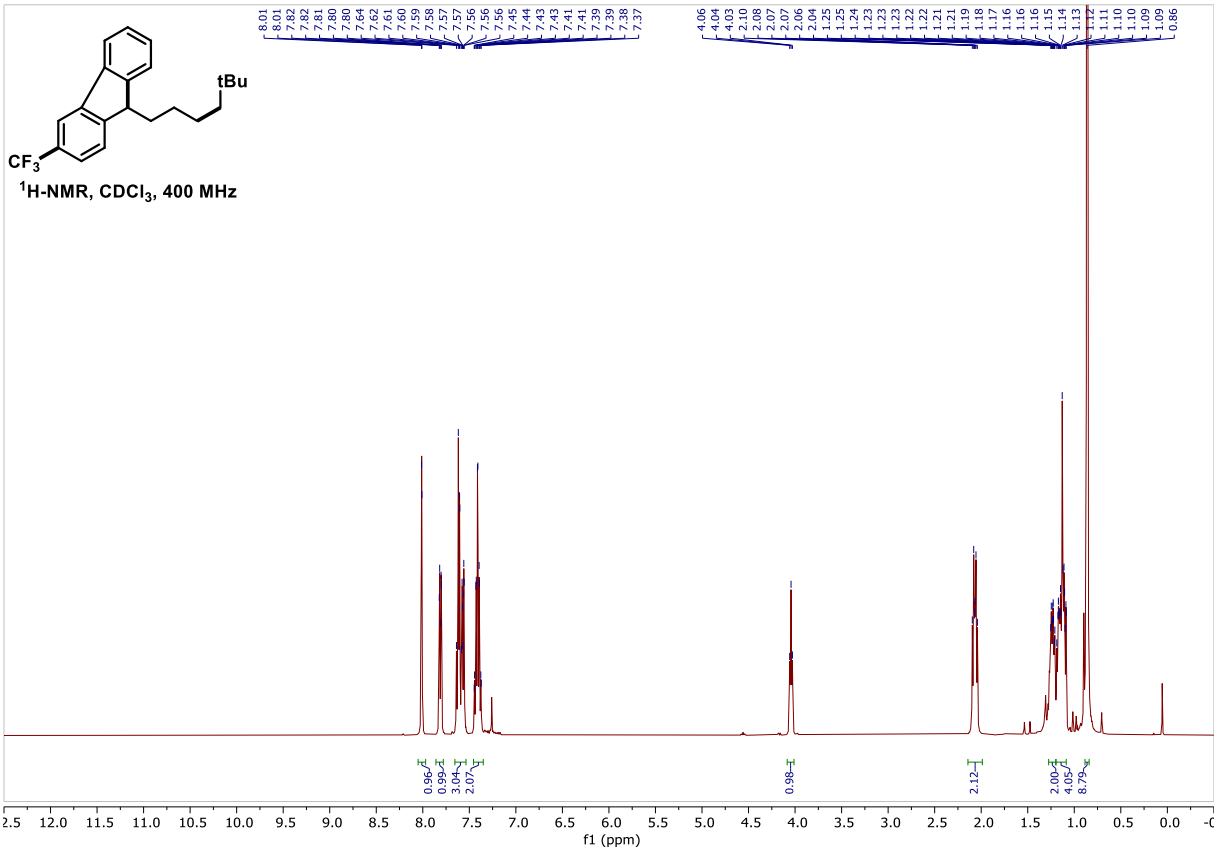


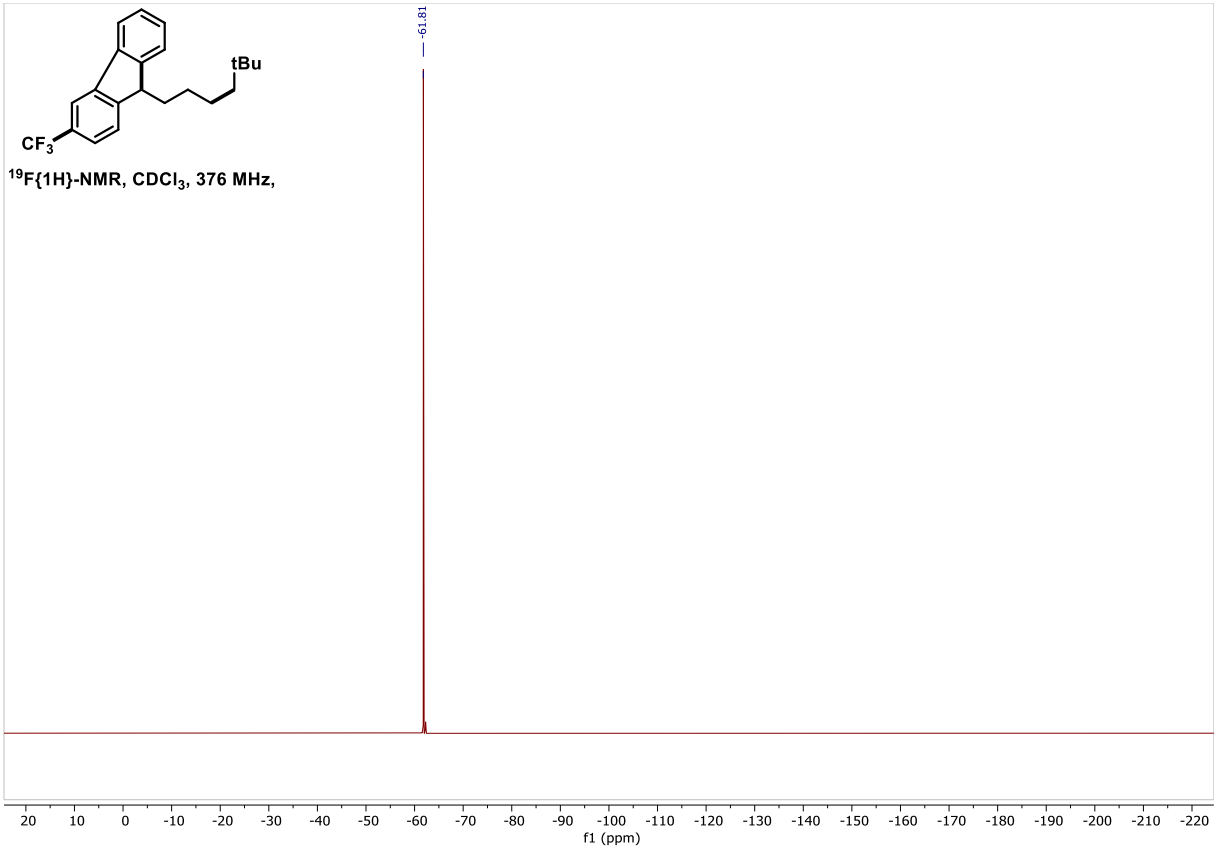
1-Chloro-2-(1-(4-methoxyphenyl)-5,5-dimethylhexyl)benzene (**3.3g**)



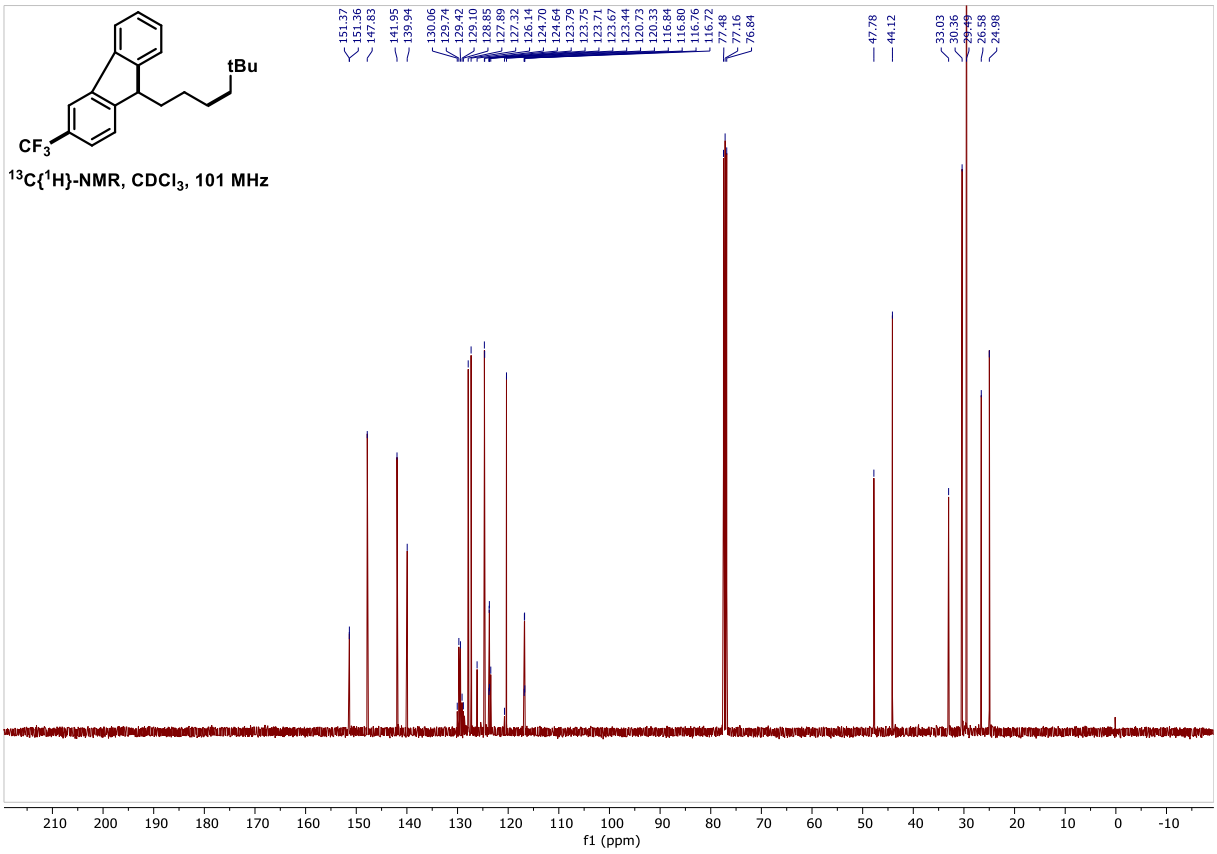


9-(5,5-Dimethylhexyl)-3-(trifluoromethyl)-9H-fluorene (**3.25b**)



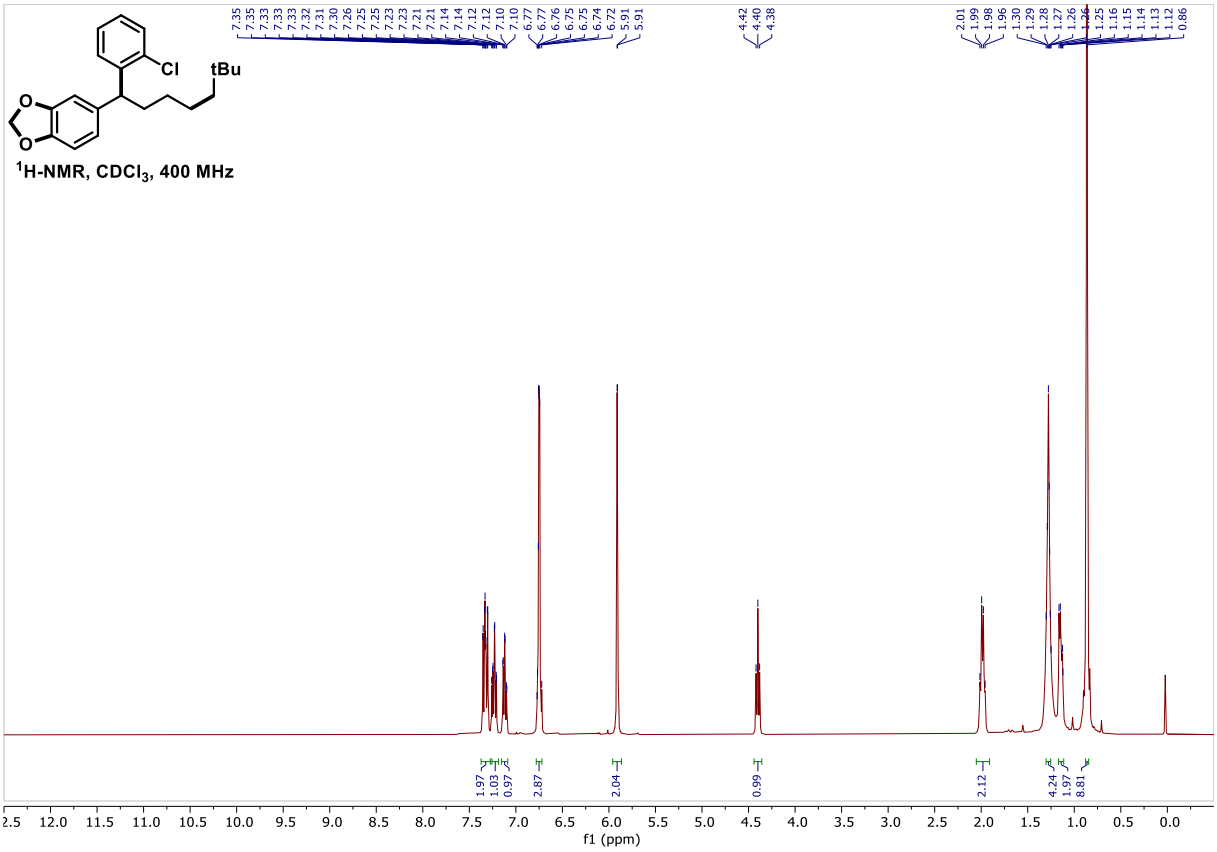


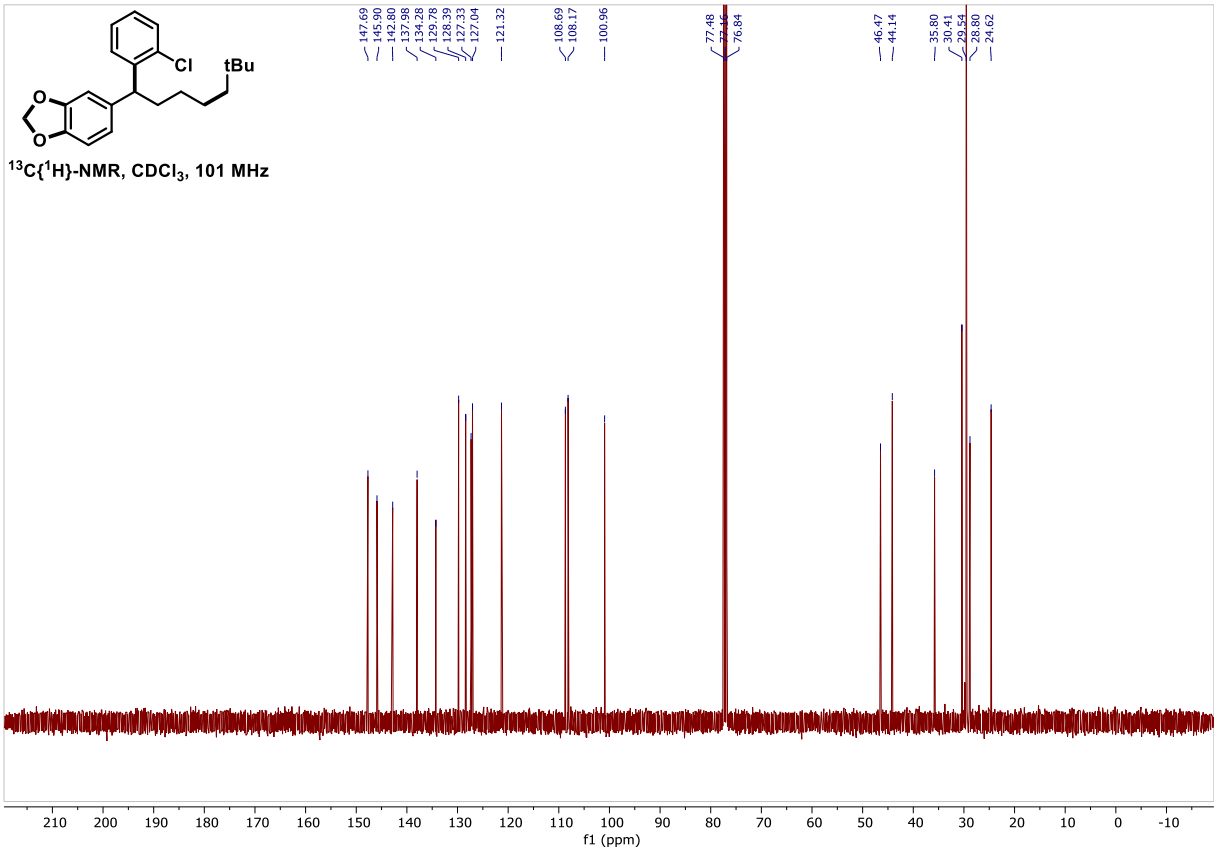
$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 376 MHz,



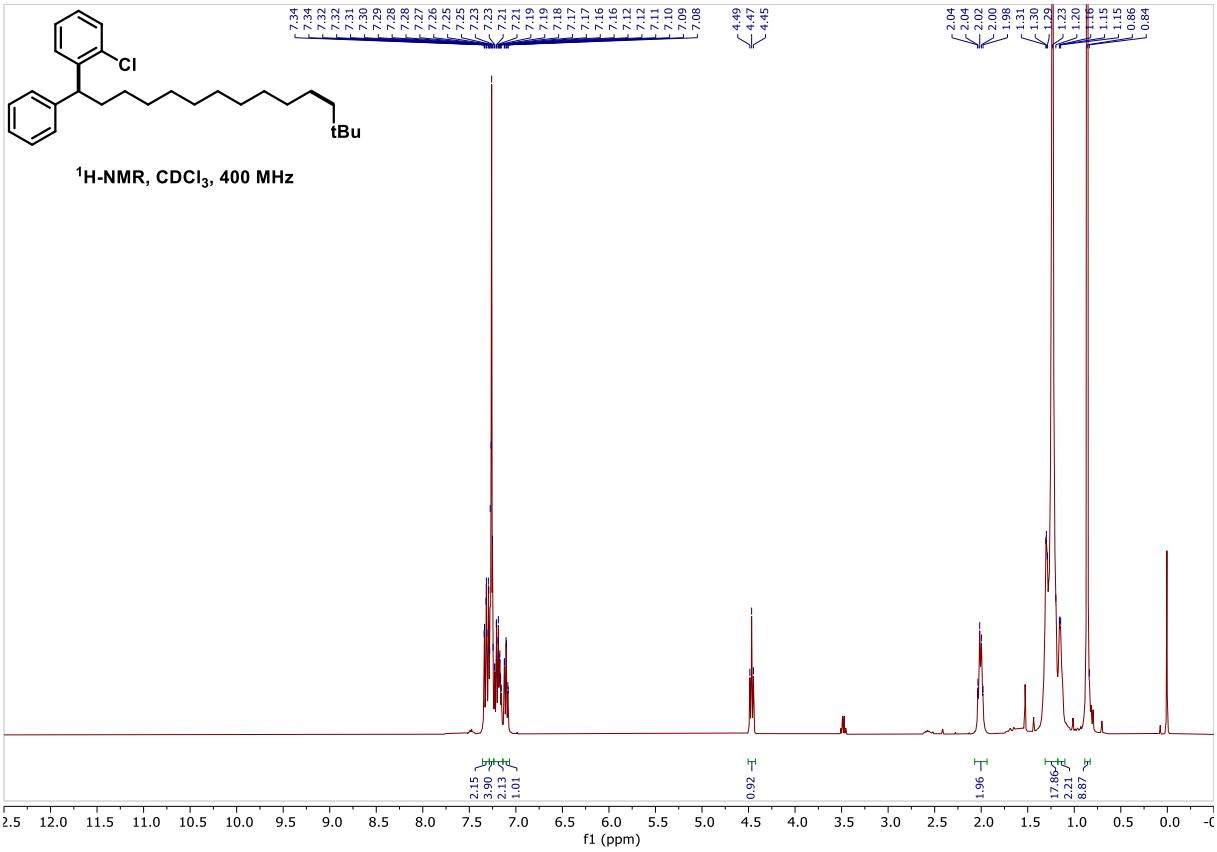
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 101 MHz

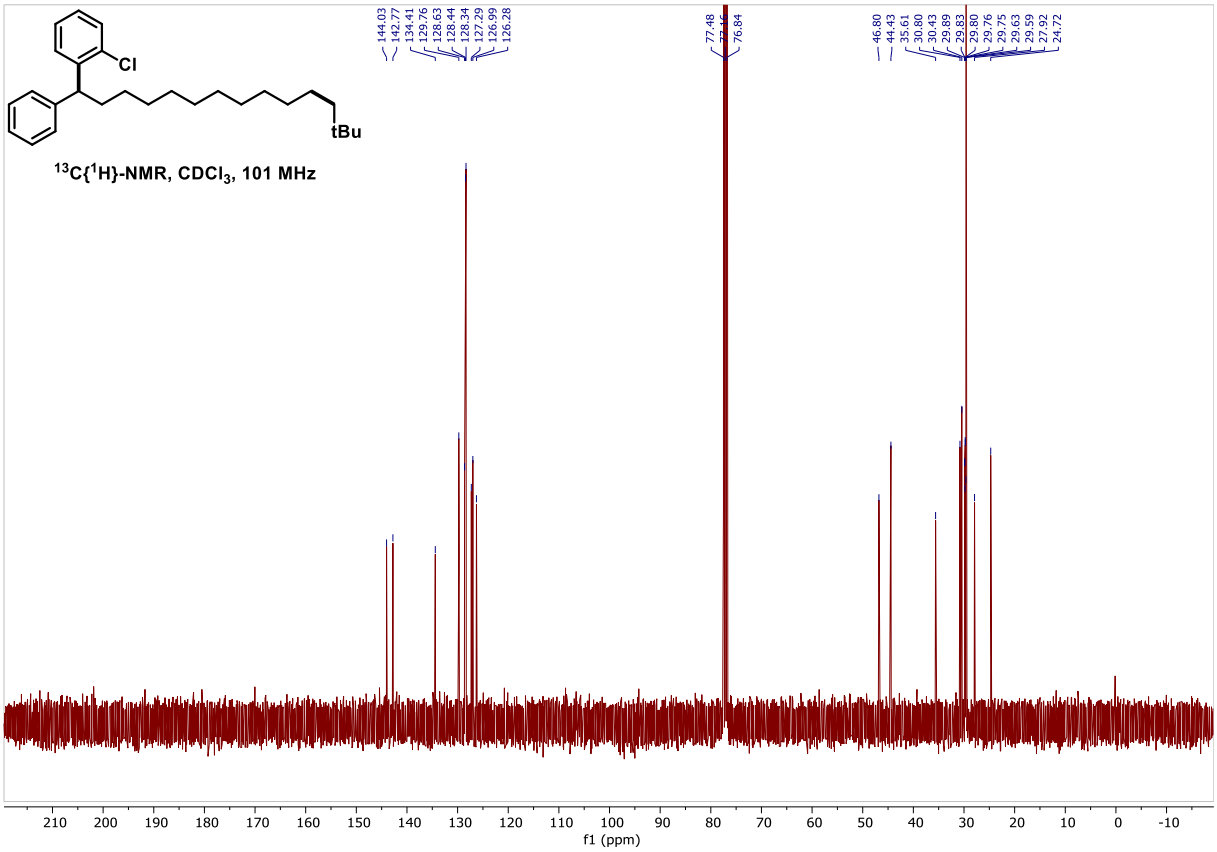
5-(1-(2-Chlorophenyl)-6,6-dimethylheptyl)benzo-1,3-dioxole (**3.3i**)



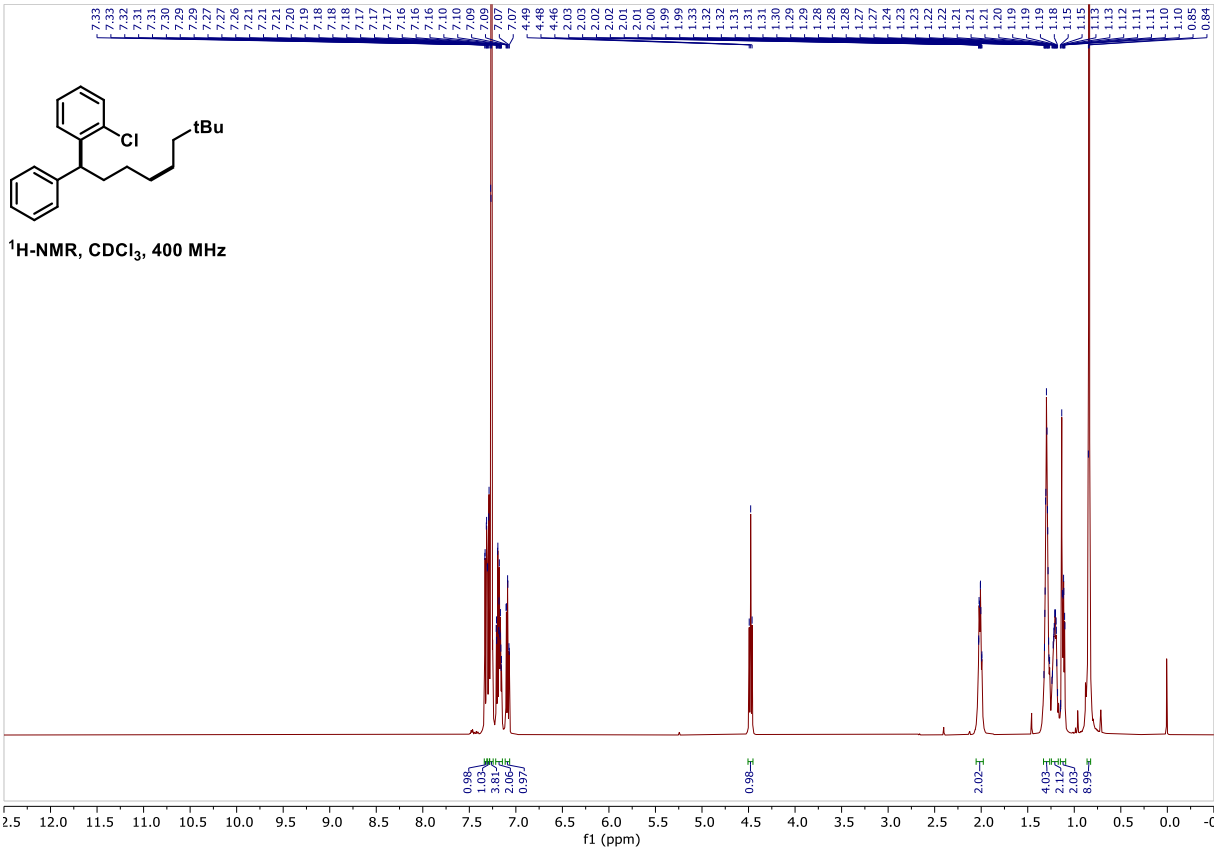


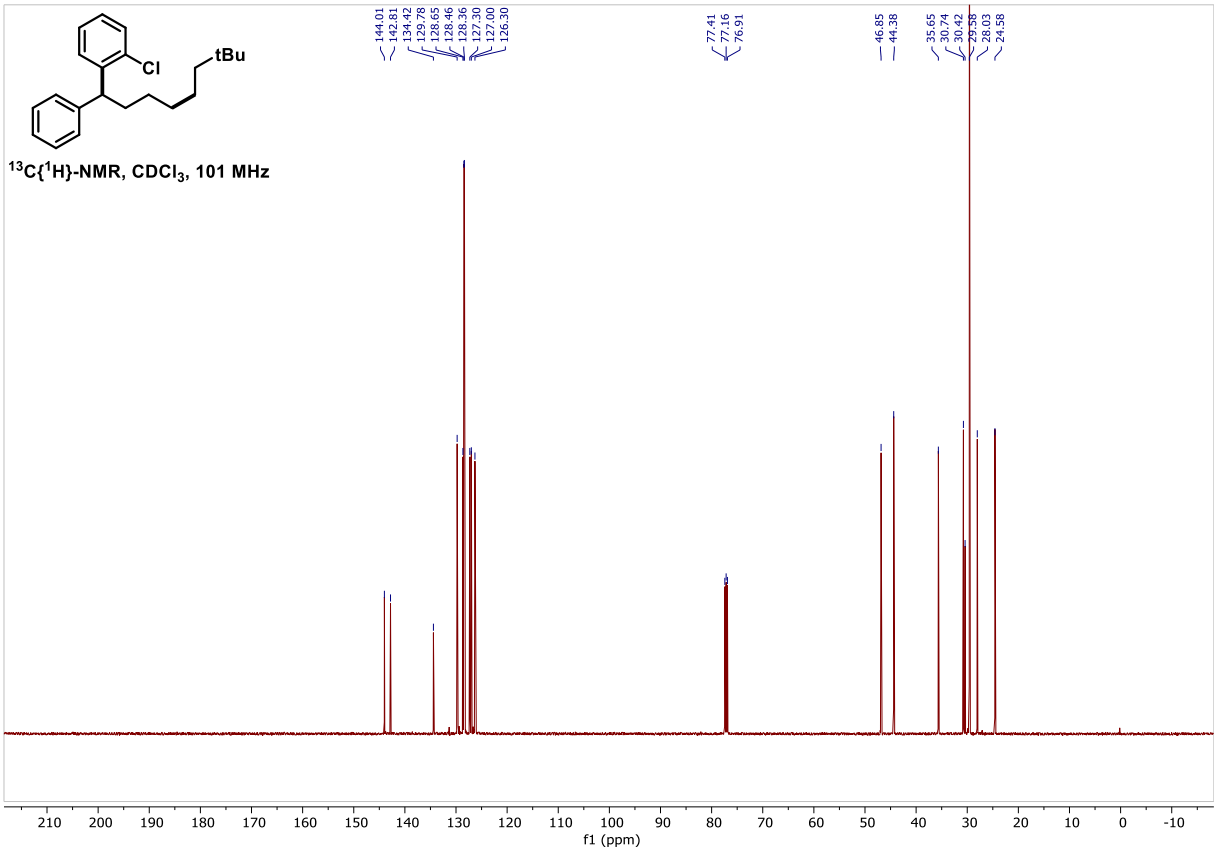
1-Chloro-2-(13,13-dimethyl-1-phenyltetradecyl)benzene (**3.3j**)



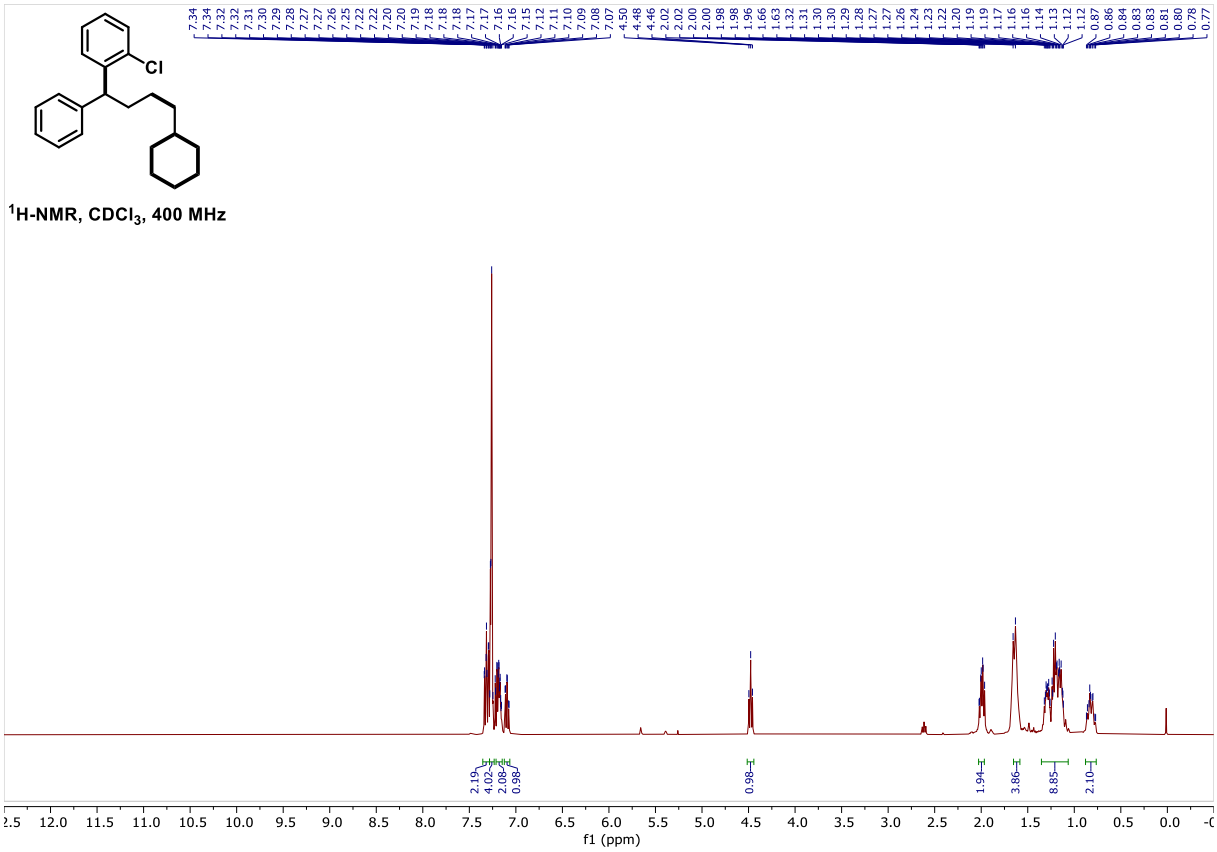


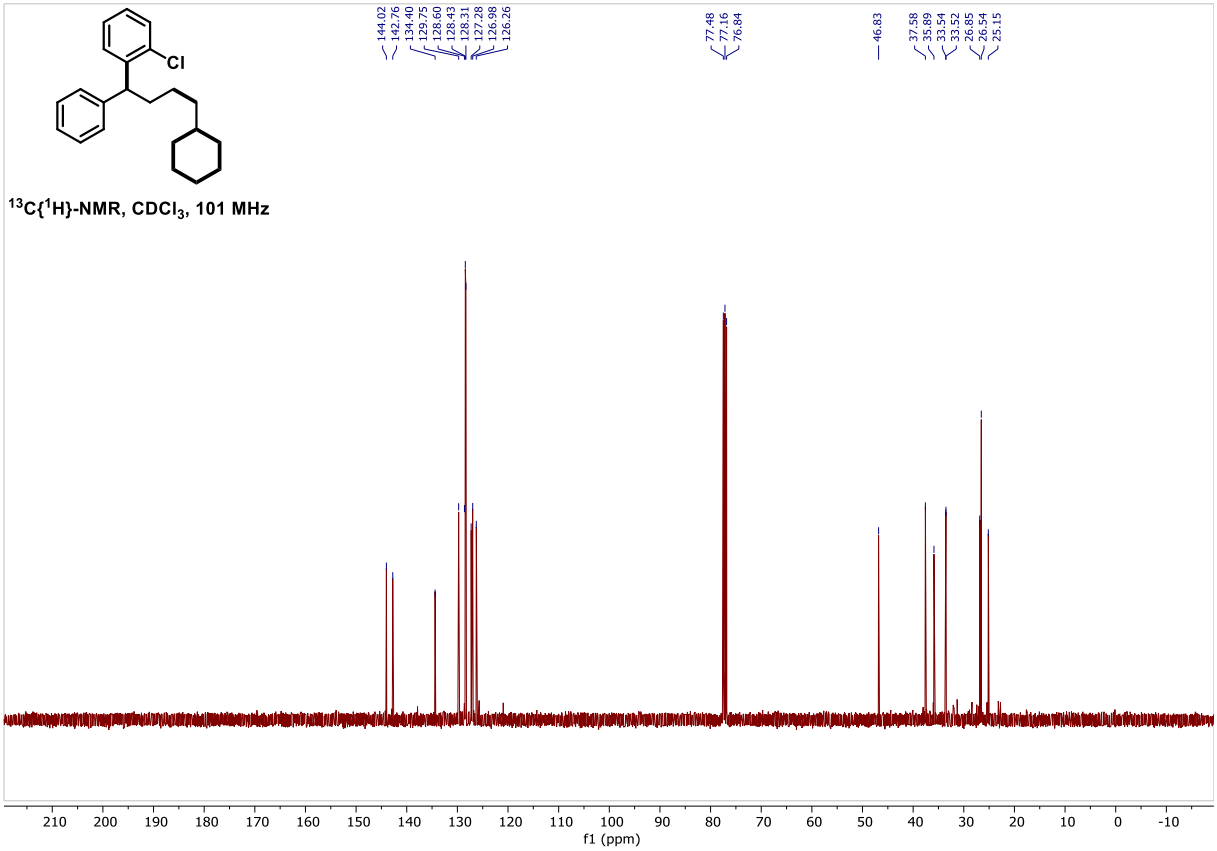
1-Chloro-2-(7,7-dimethyl-1-phenyloctyl)benzene (**3.3k**)



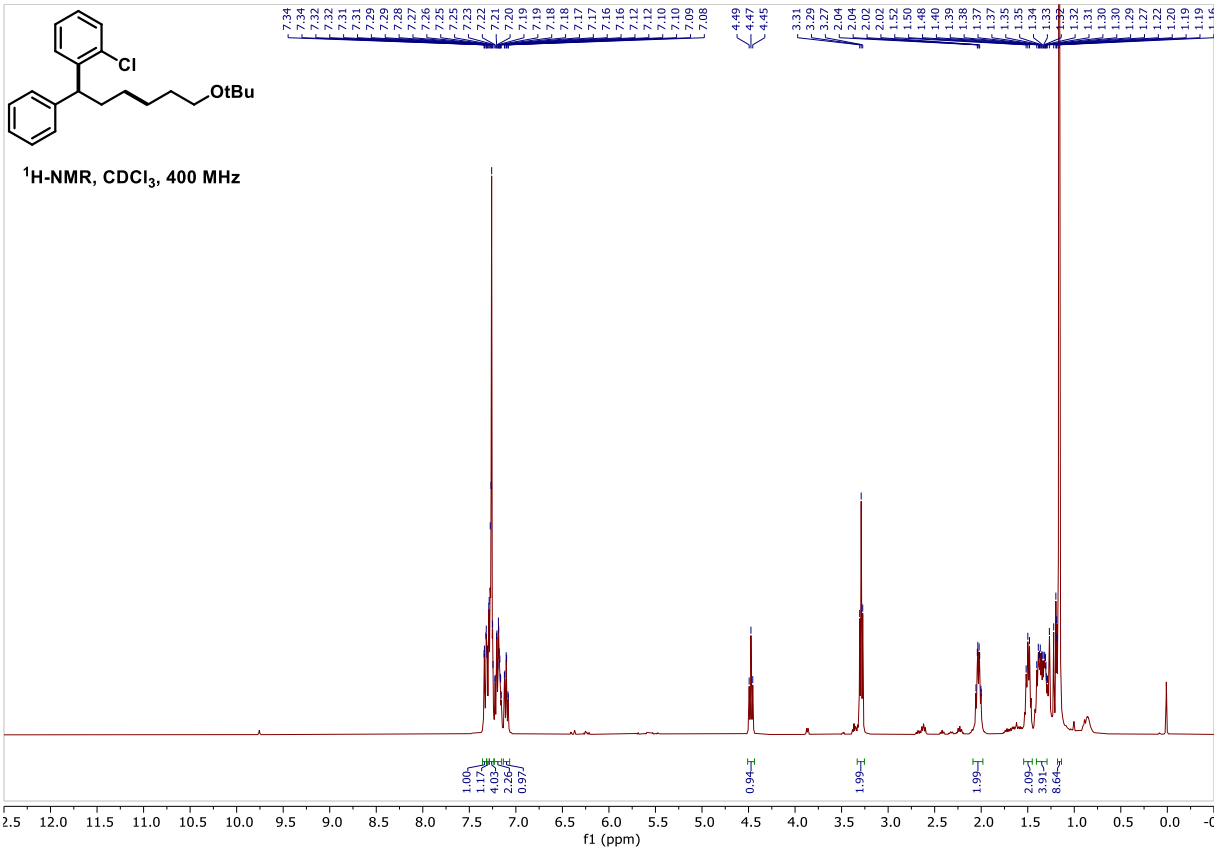


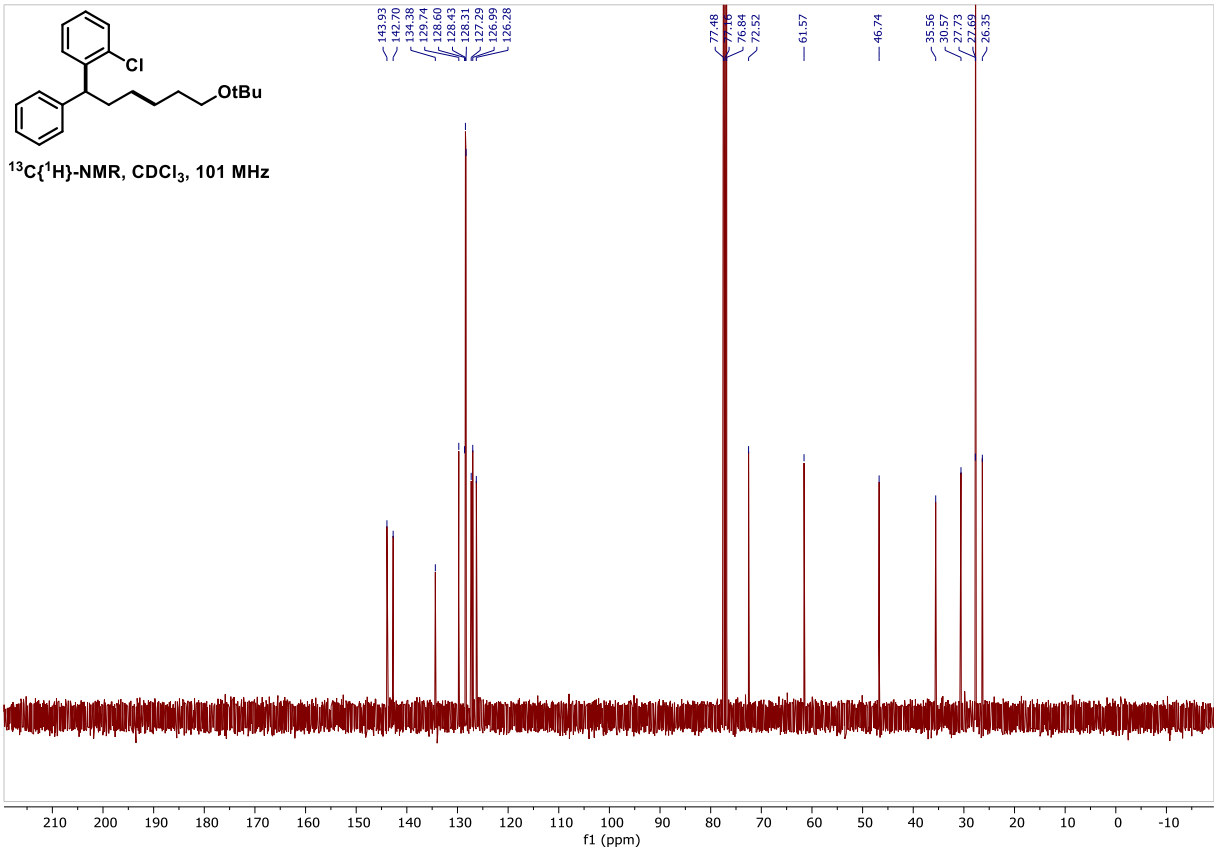
1-Chloro-2-(4-cyclohexyl-1-phenylbutyl)benzene (**3.3l**)



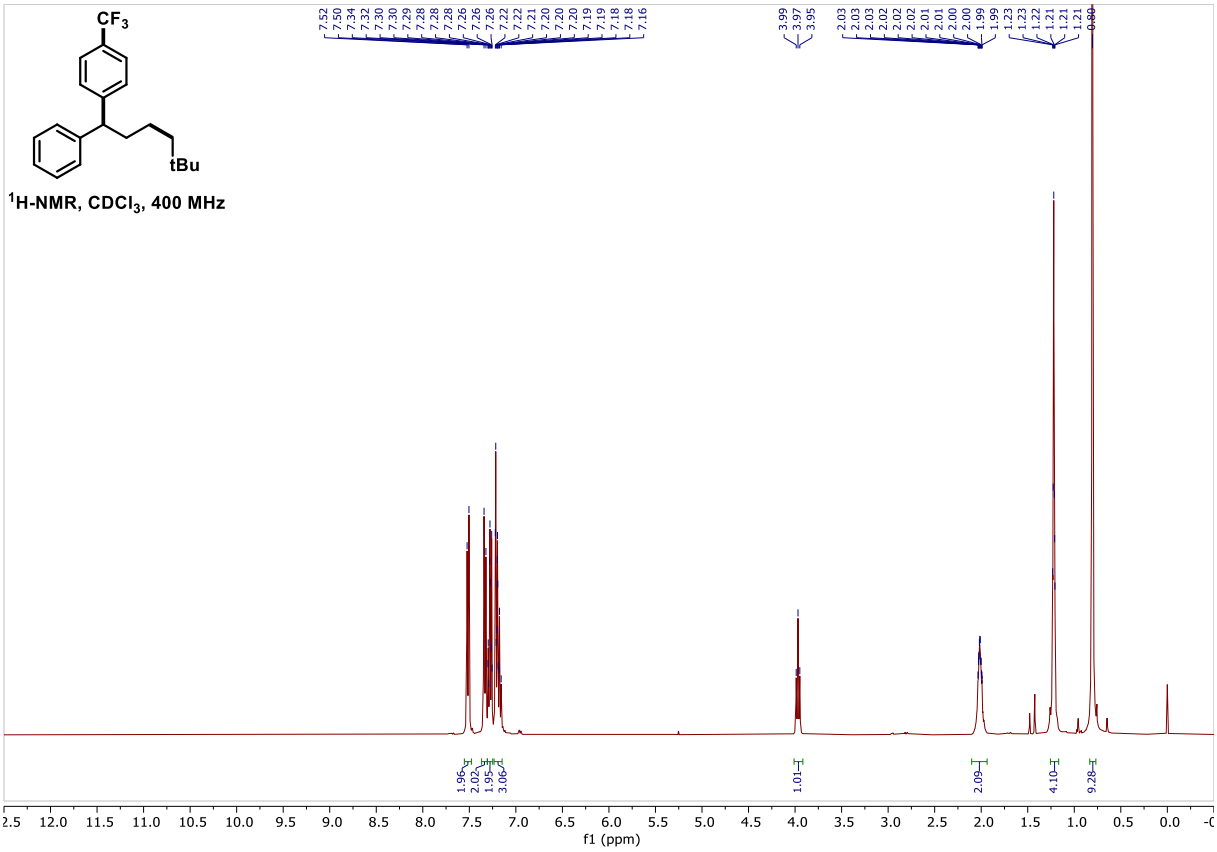


1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chlorobenzene (**3.3b**)

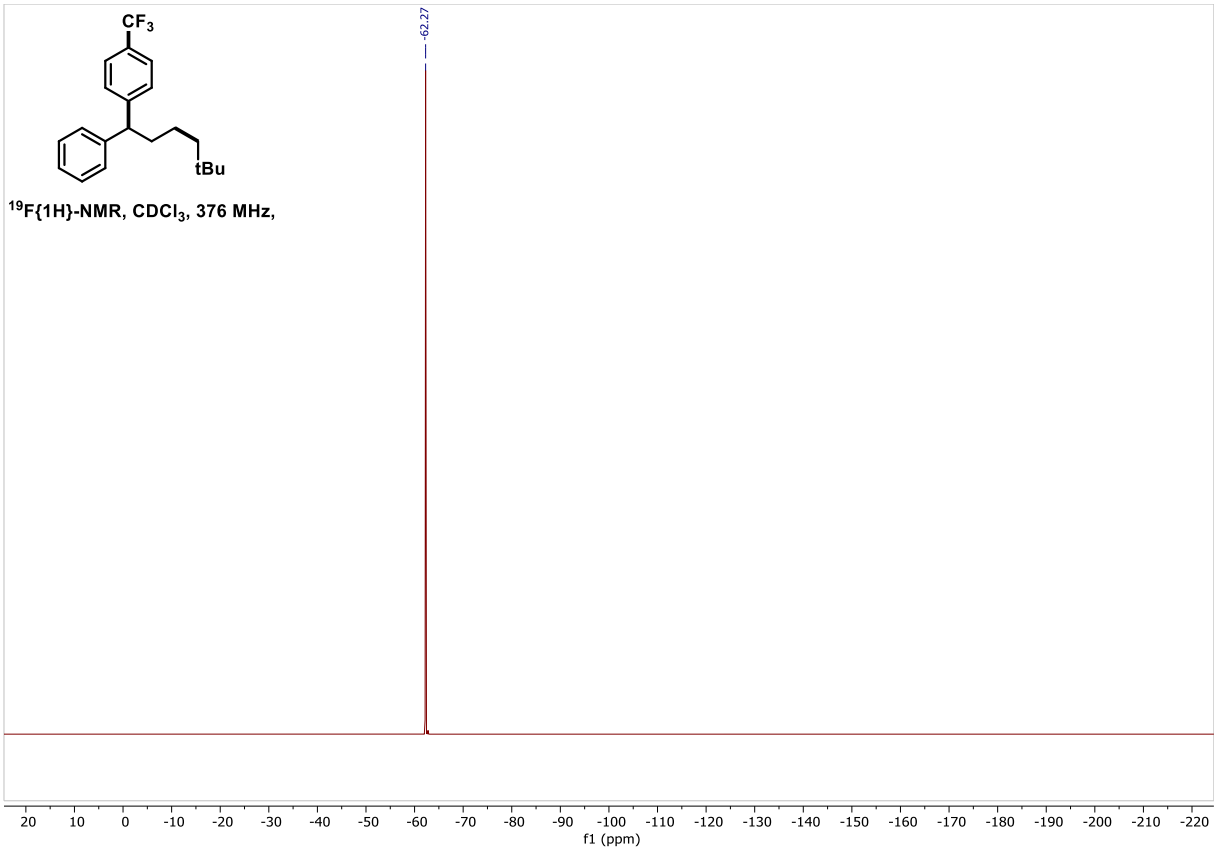




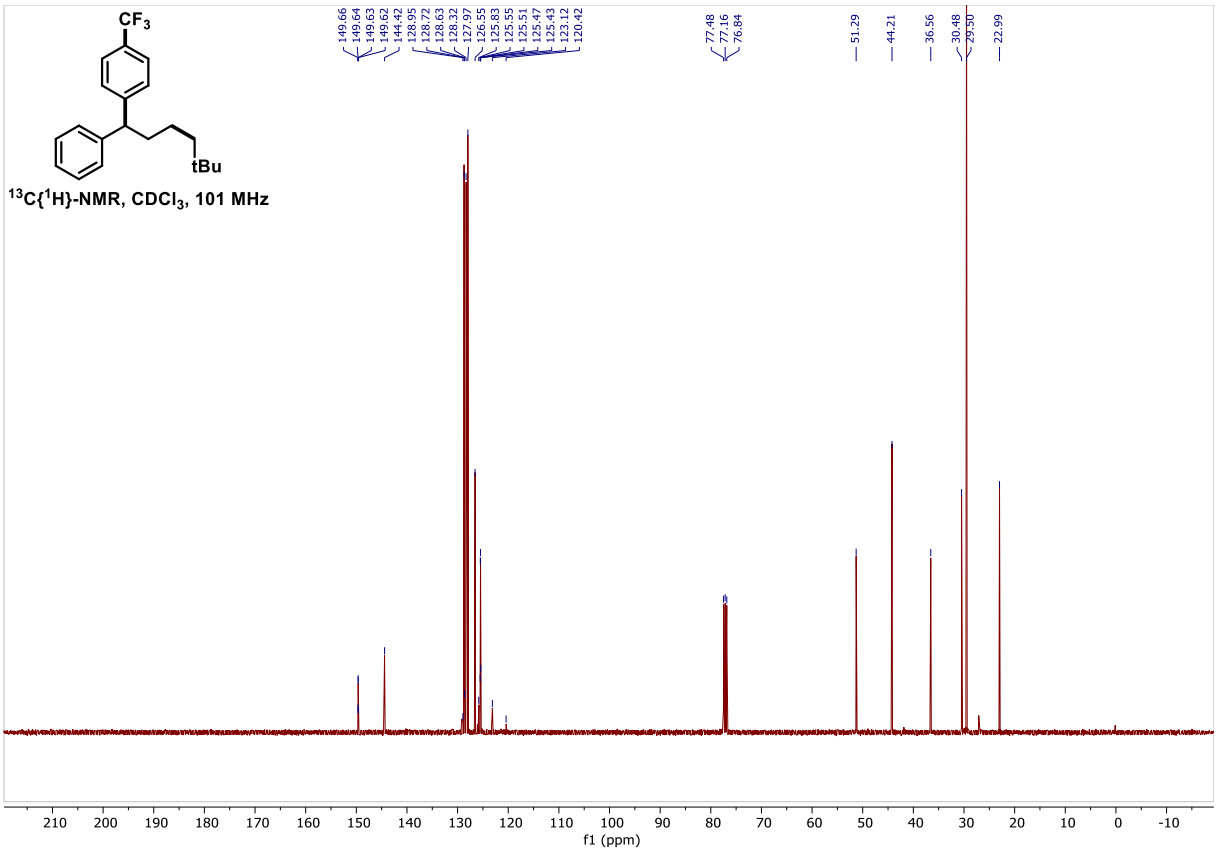
1-(5,5-Dimethyl-1-phenylhexyl)-4-(trifluoromethyl)benzene (**3.3m**)



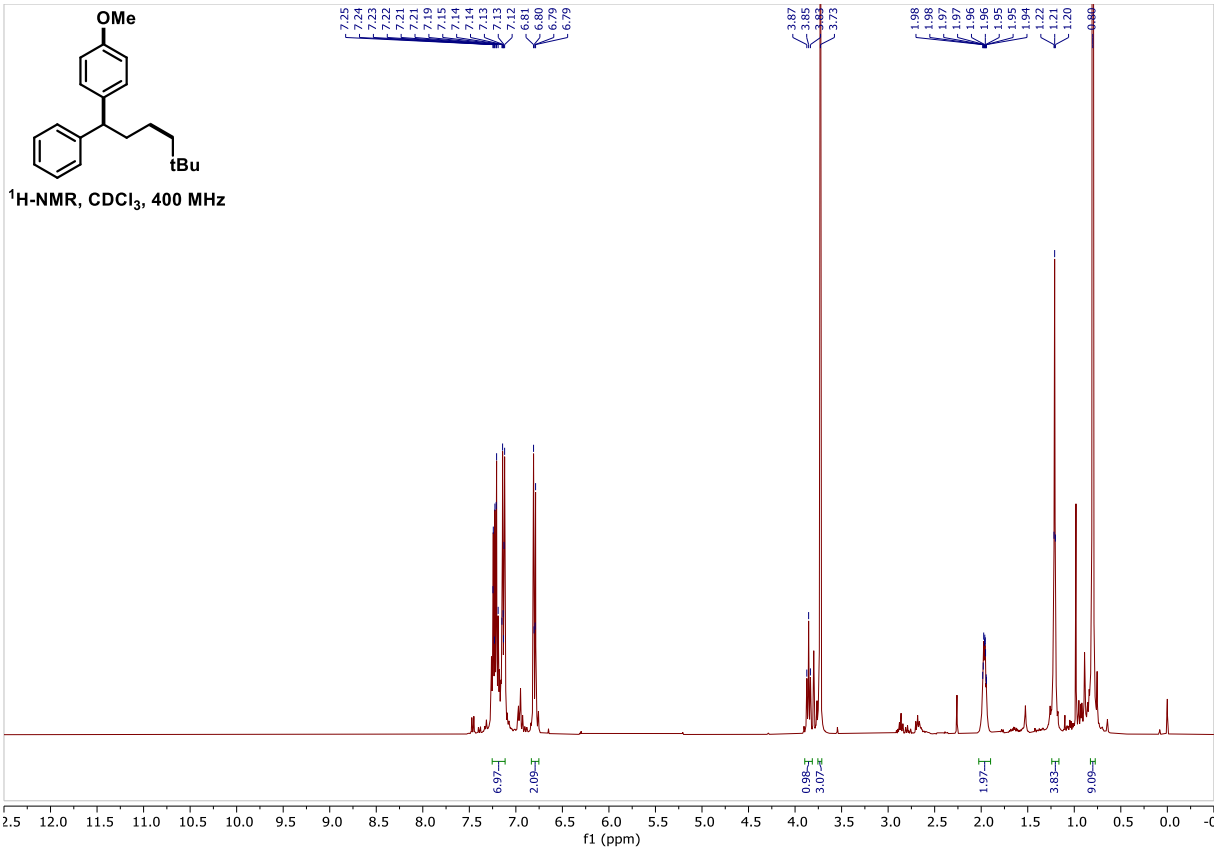
^{1}H-NMR, $CDCl_3$, 400 MHz

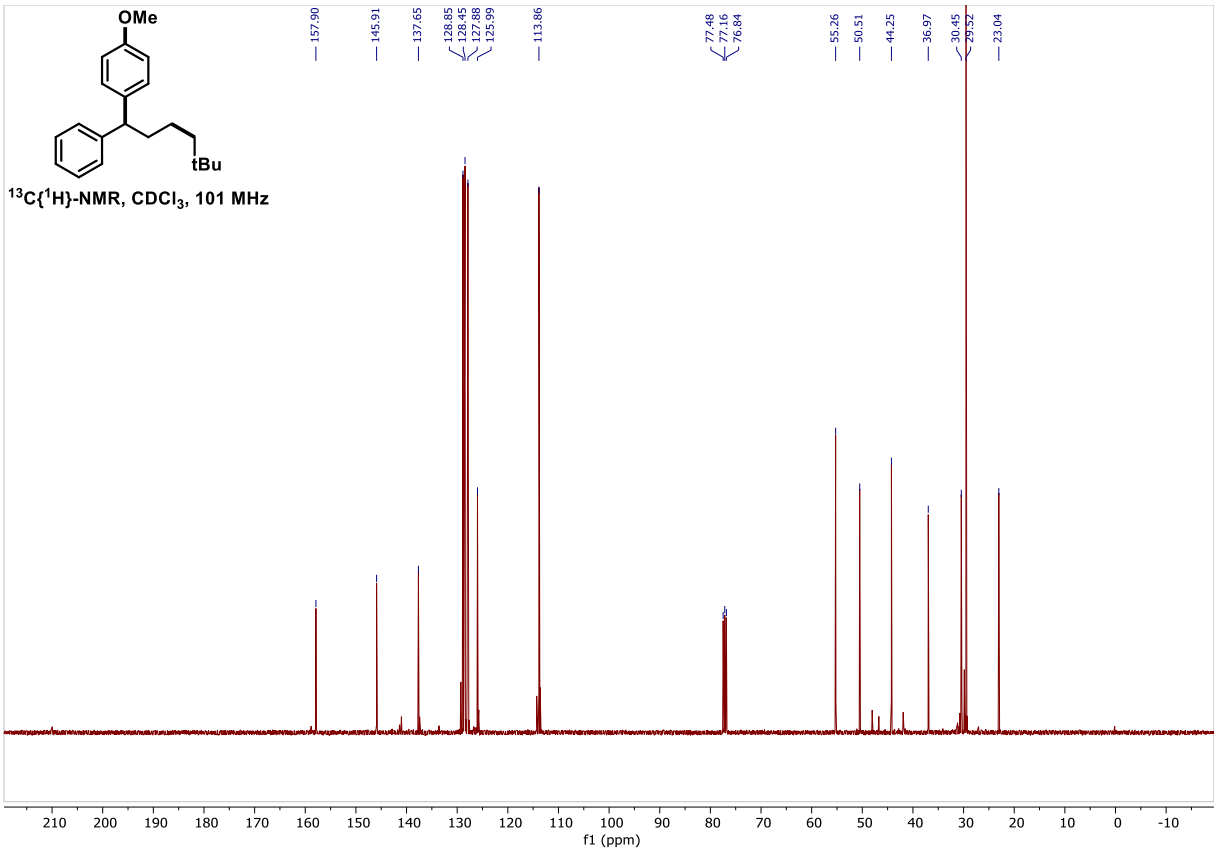


^{19}F{1H}-NMR, $CDCl_3$, 376 MHz,

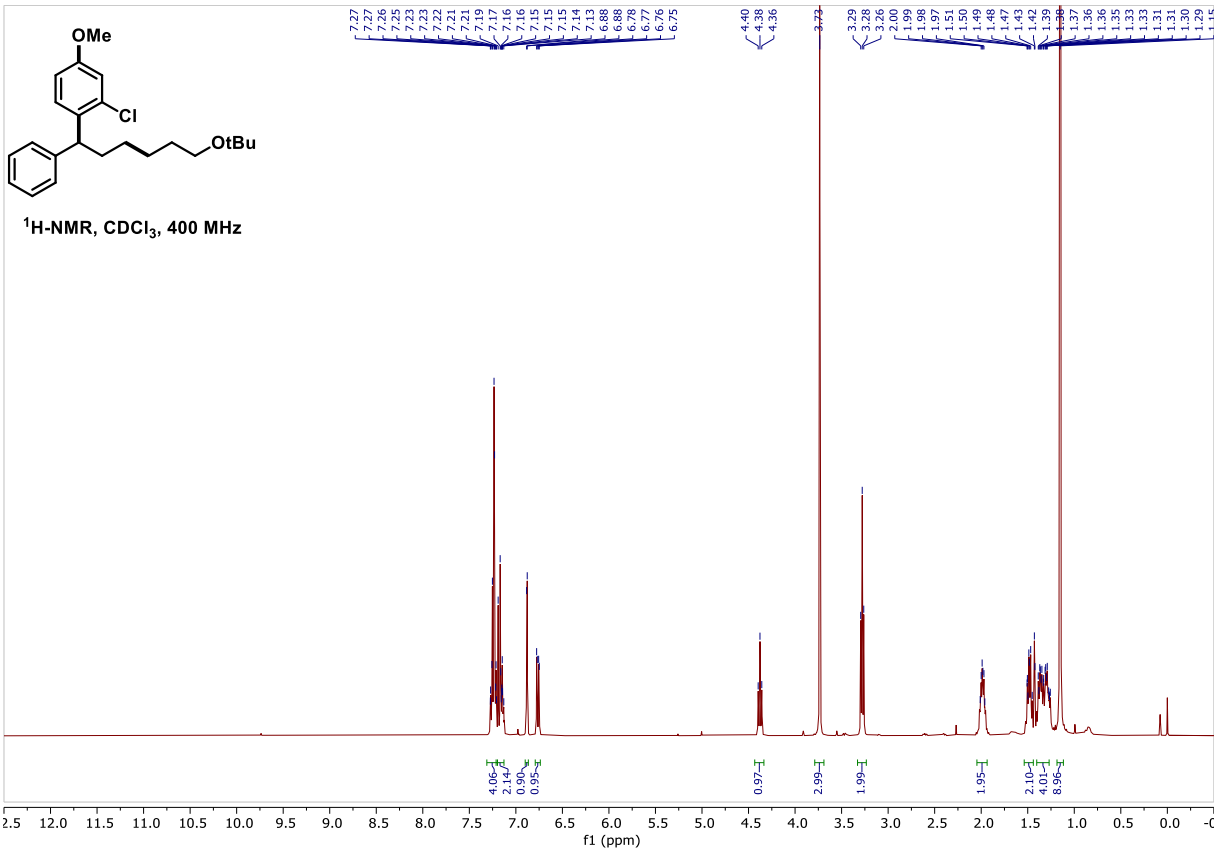


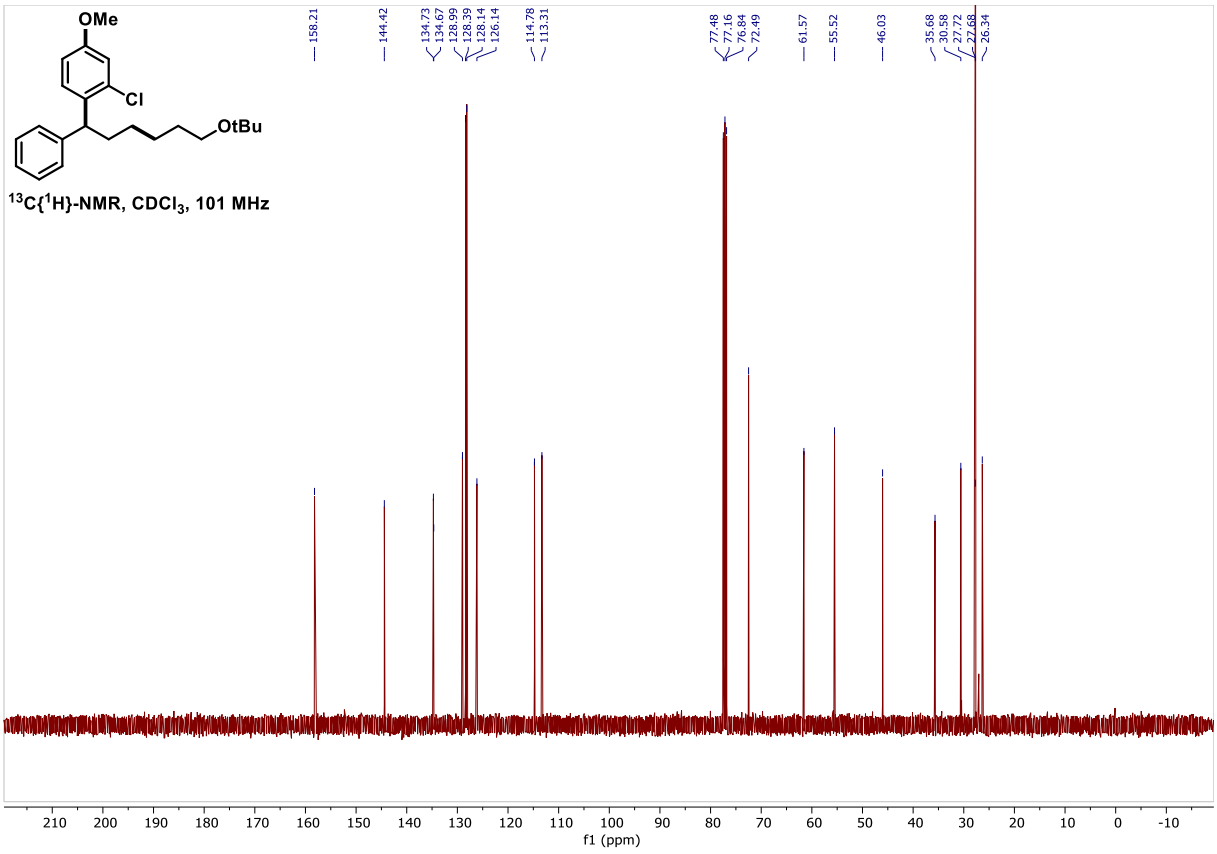
1-(5,5-Dimethyl-1-phenylhexyl)-4-methoxybenzene (**3.3n**)



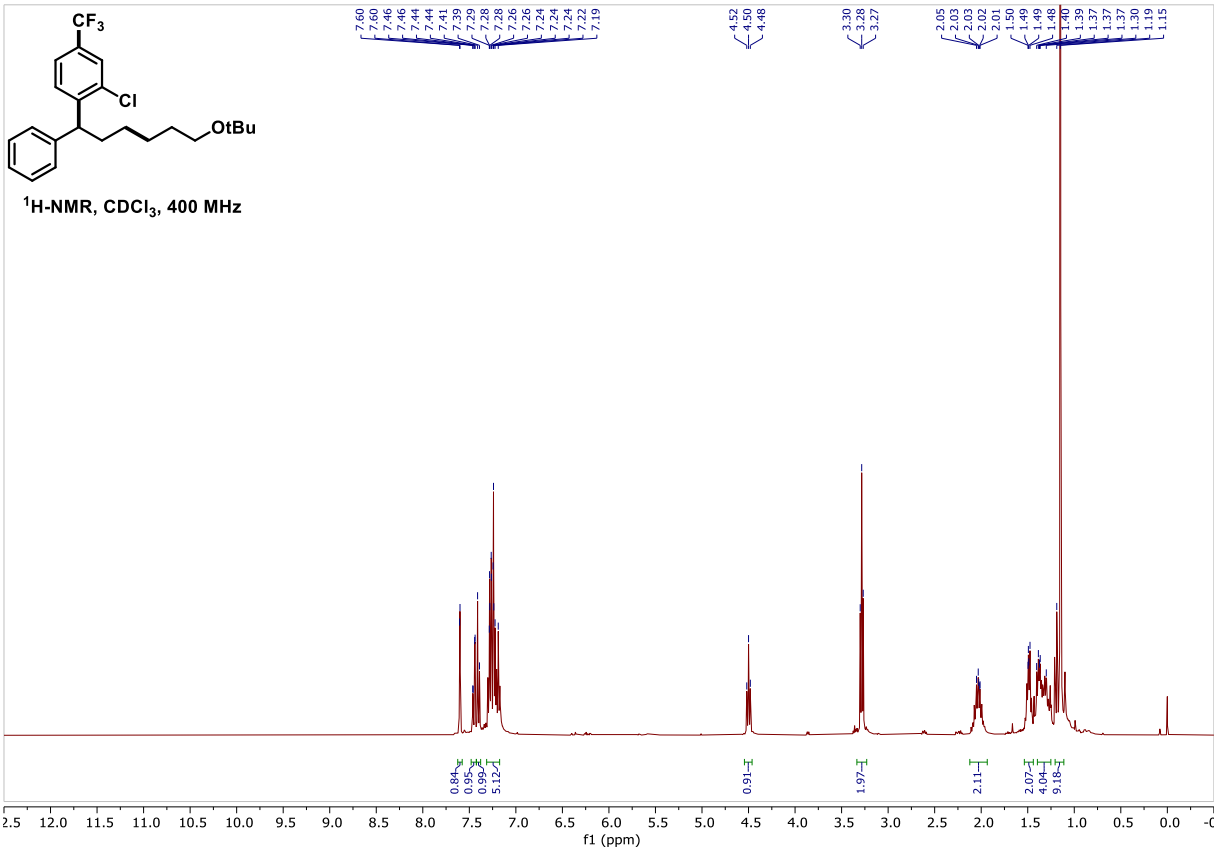


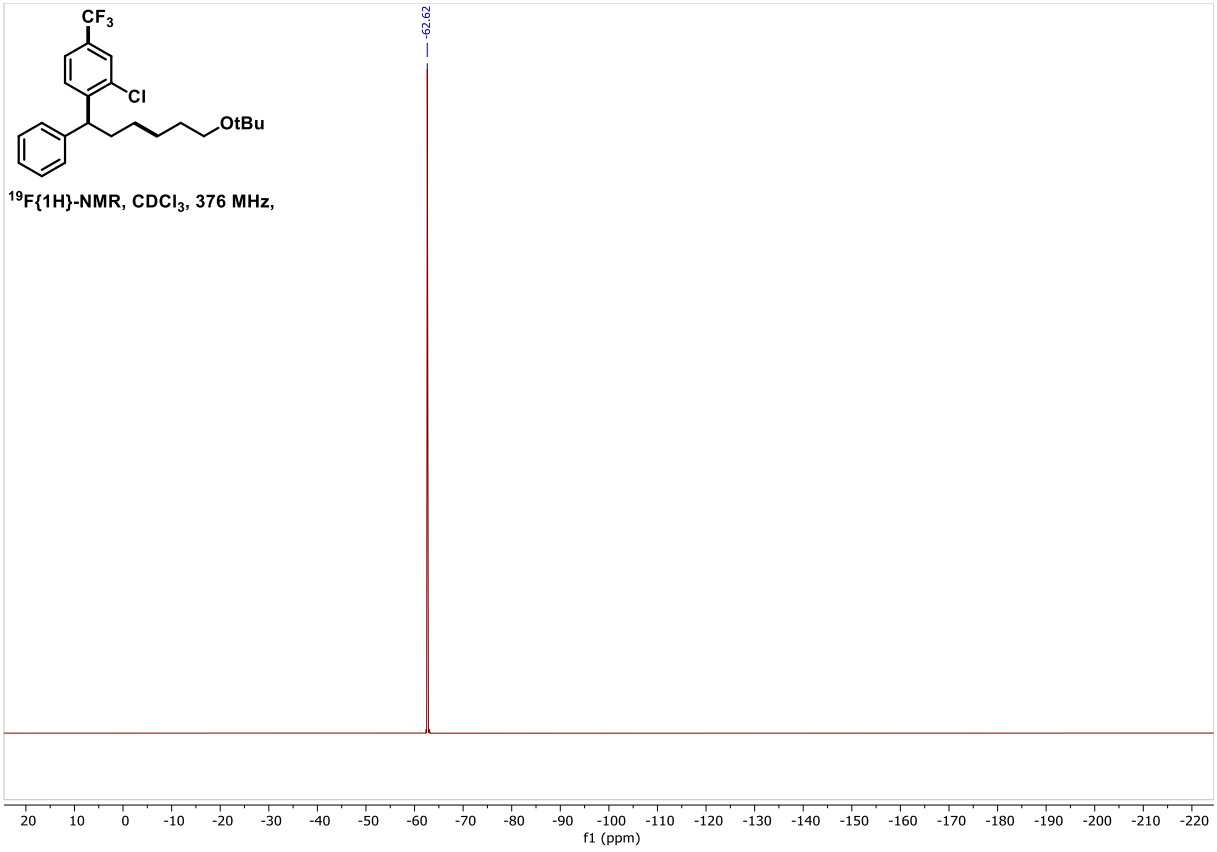
1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-4-methoxybenzene (**3.3o**)



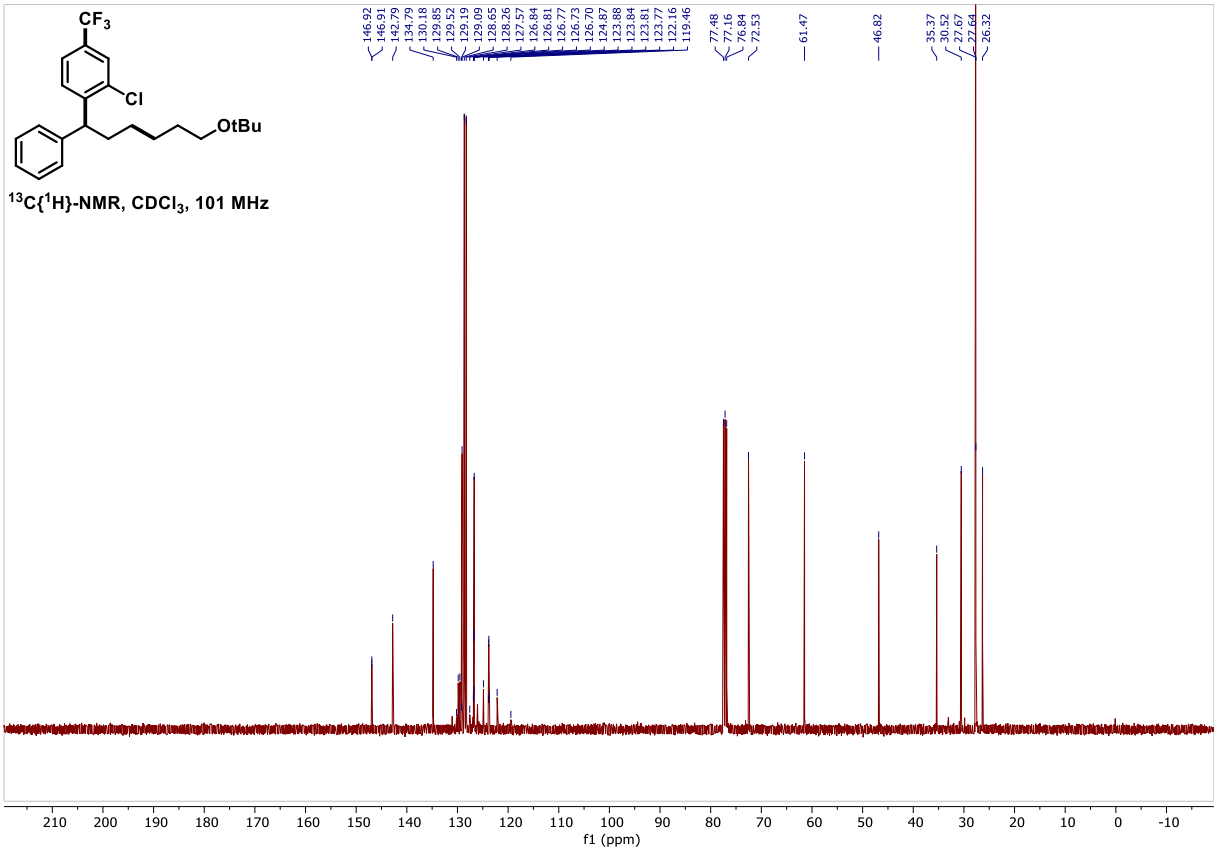


1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-4-(trifluoromethyl)benzene (**3.3p**)



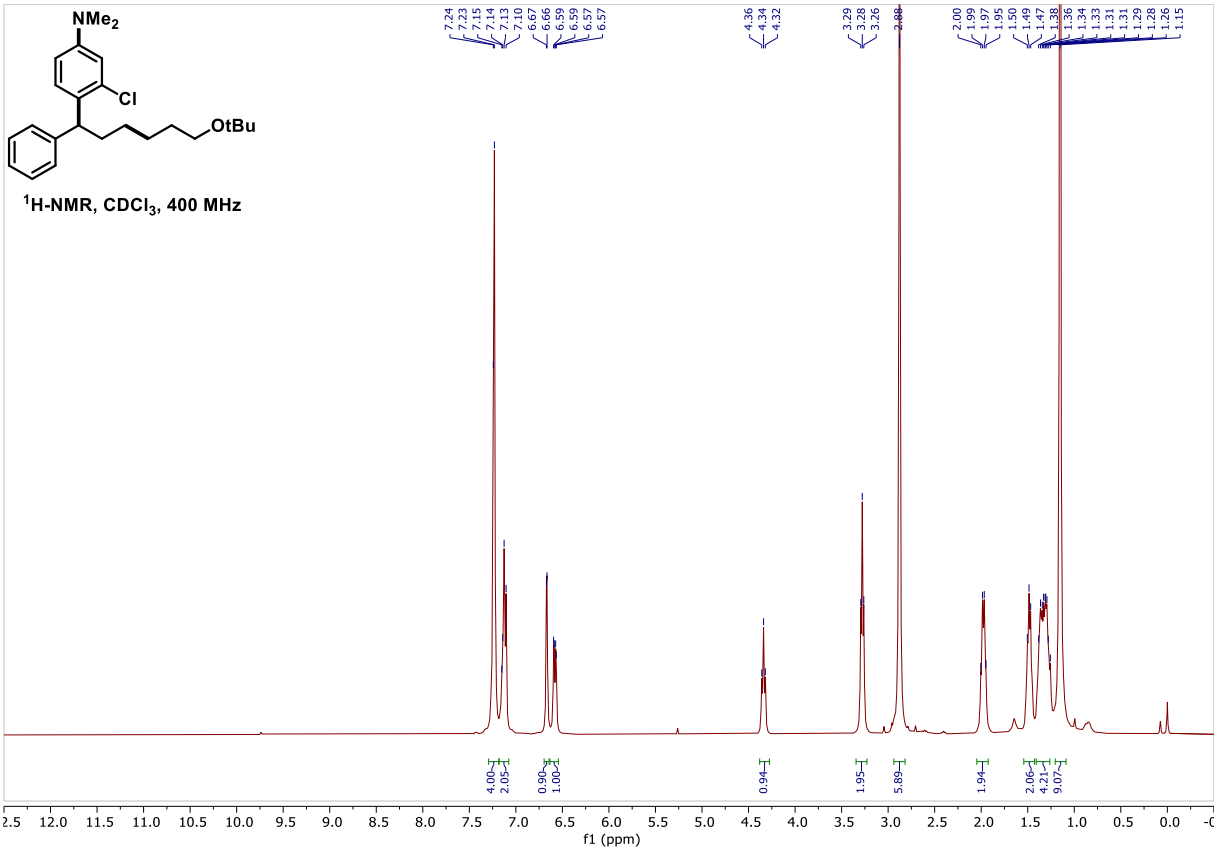


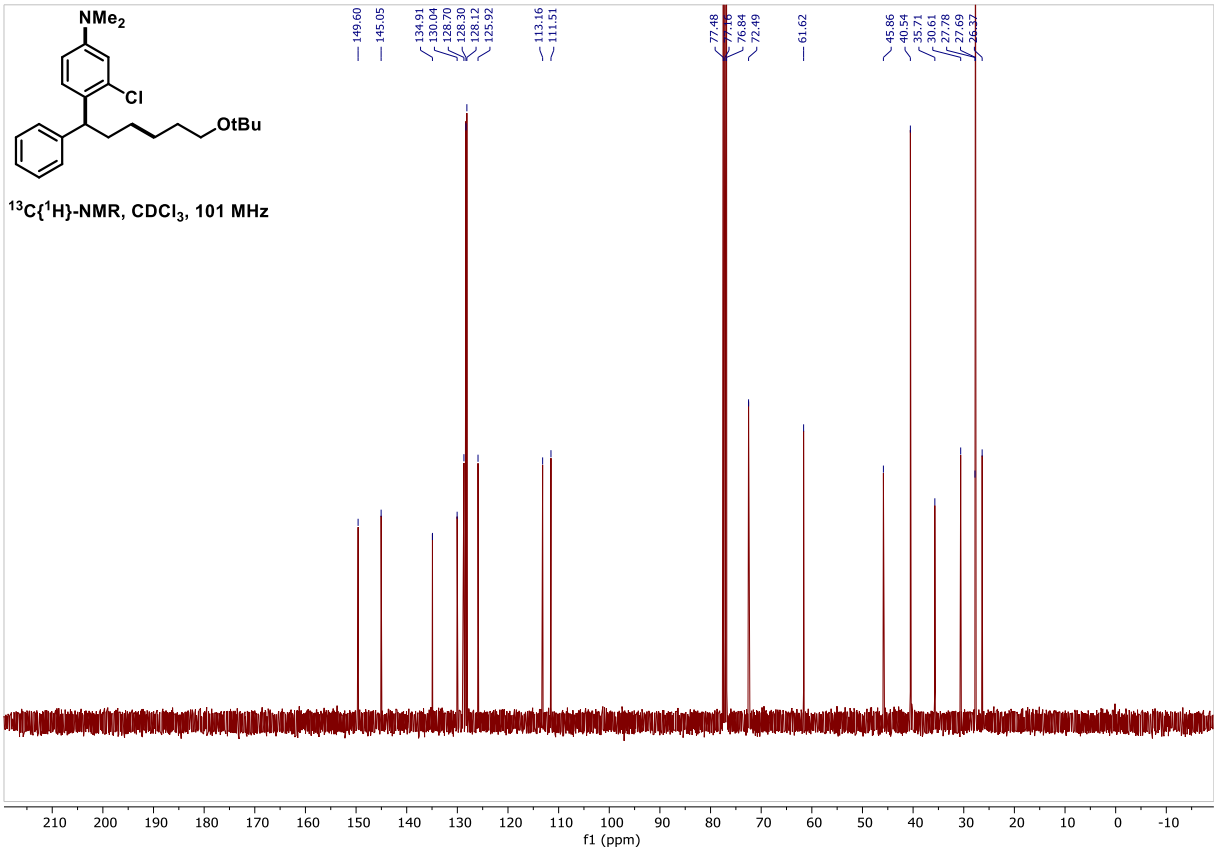
$^{19}F\{1H\}$-NMR, $CDCl_3$, 376 MHz,



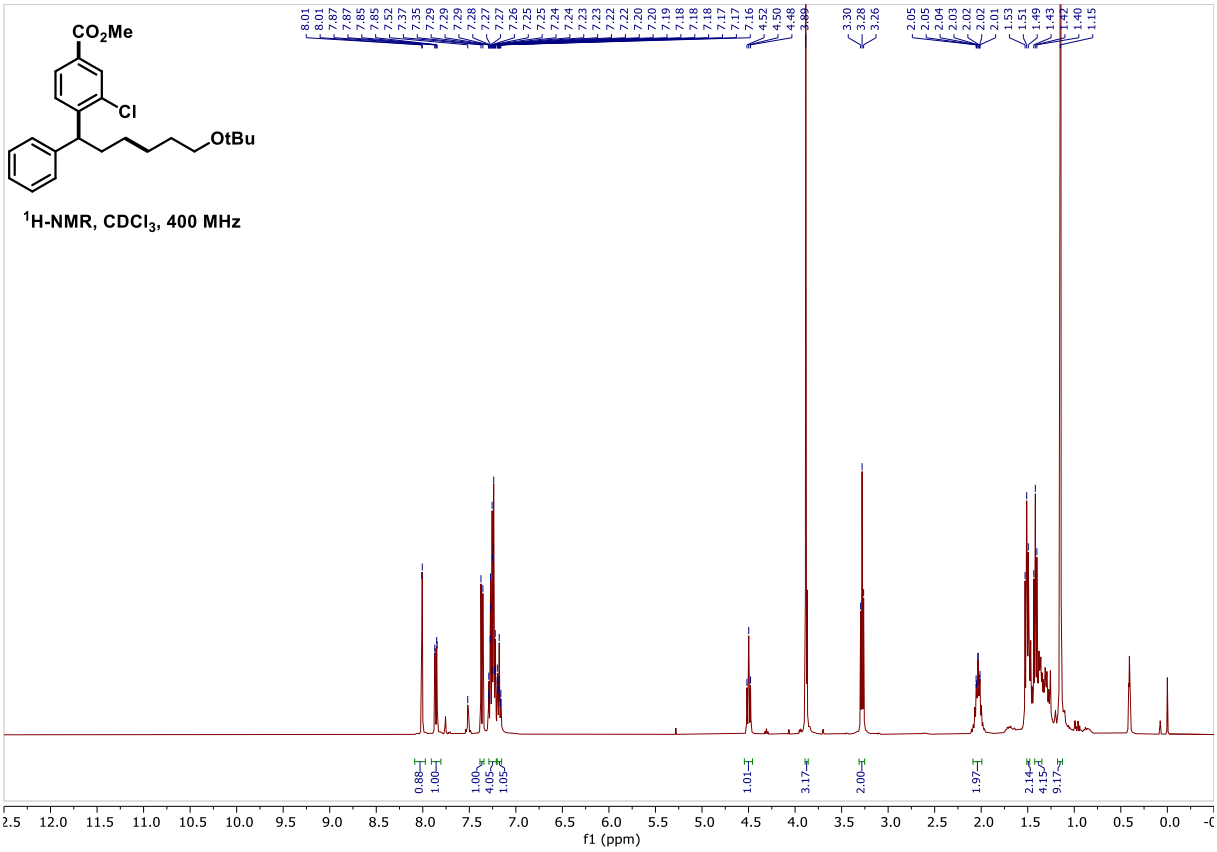
$^{13}C\{^1H\}$-NMR, $CDCl_3$, 101 MHz

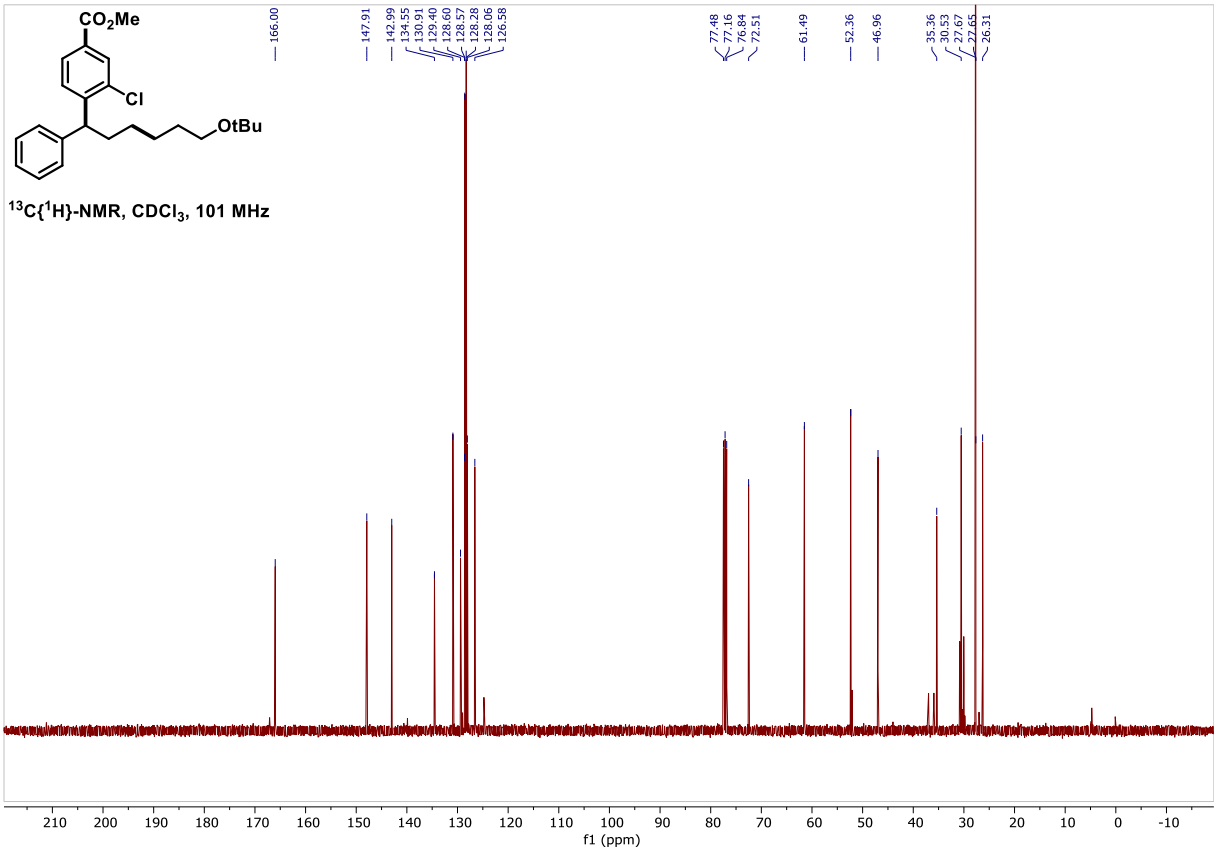
4-(6-(*tert*-Butoxy)-1-phenylhexyl)-3-chloro-N,N-dimethylaniline (**3.3q**)



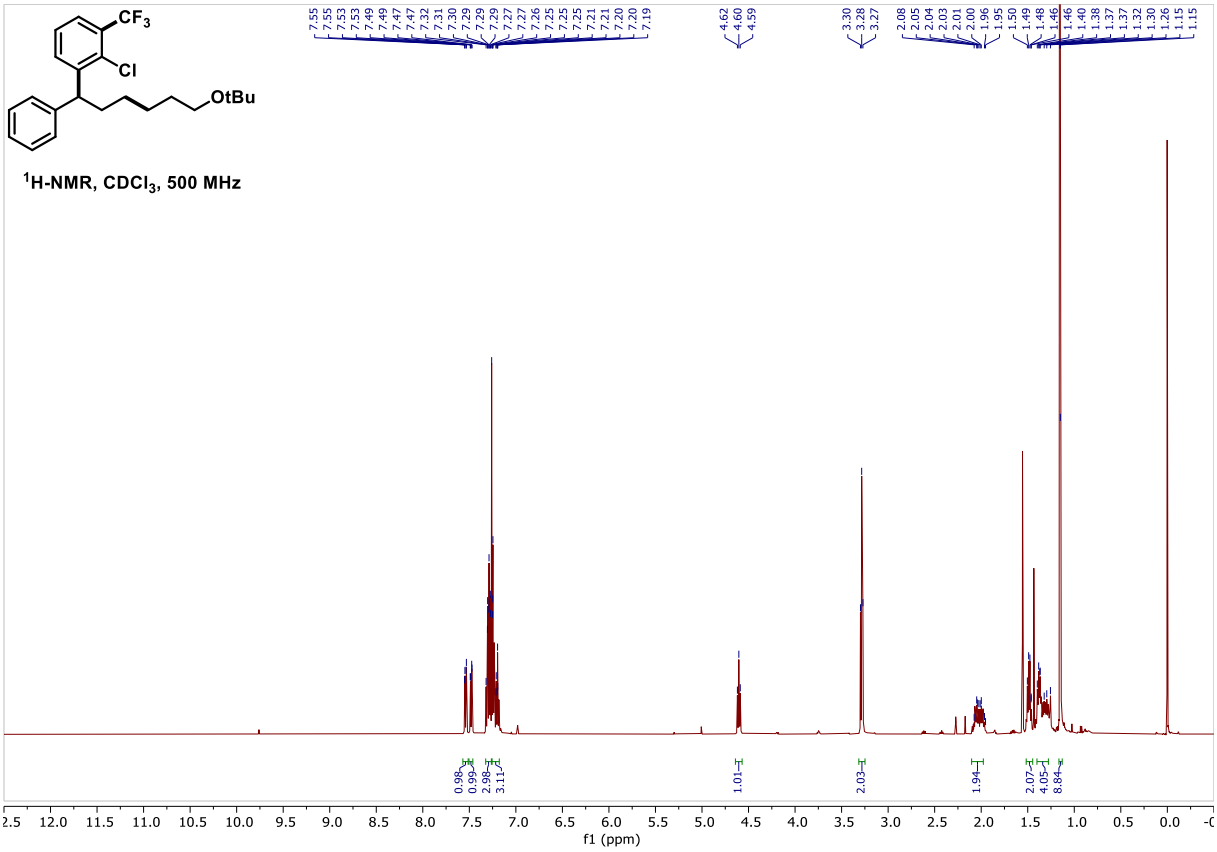


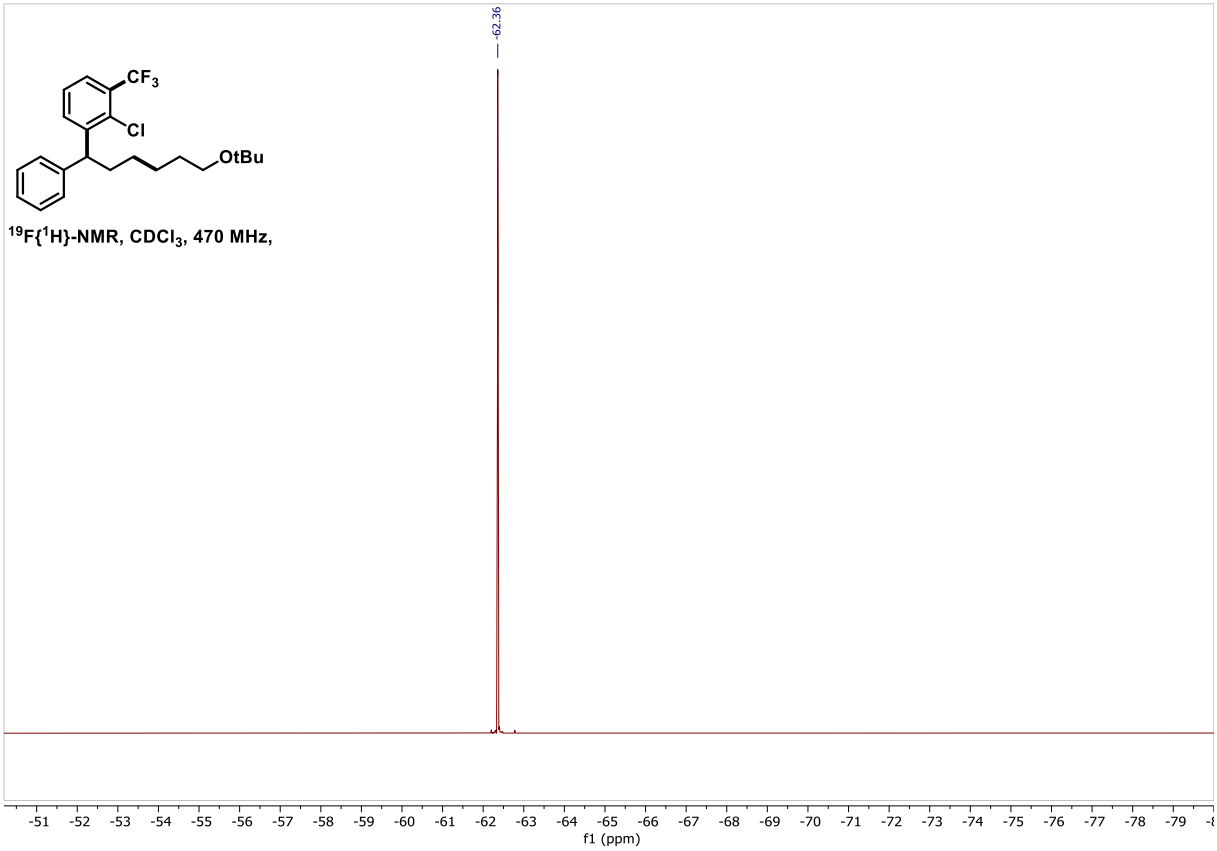
Methyl 4-(6-(*tert*-Butoxy)-1-phenylhexyl)-3-chlorobenzoate (**3.3r**)

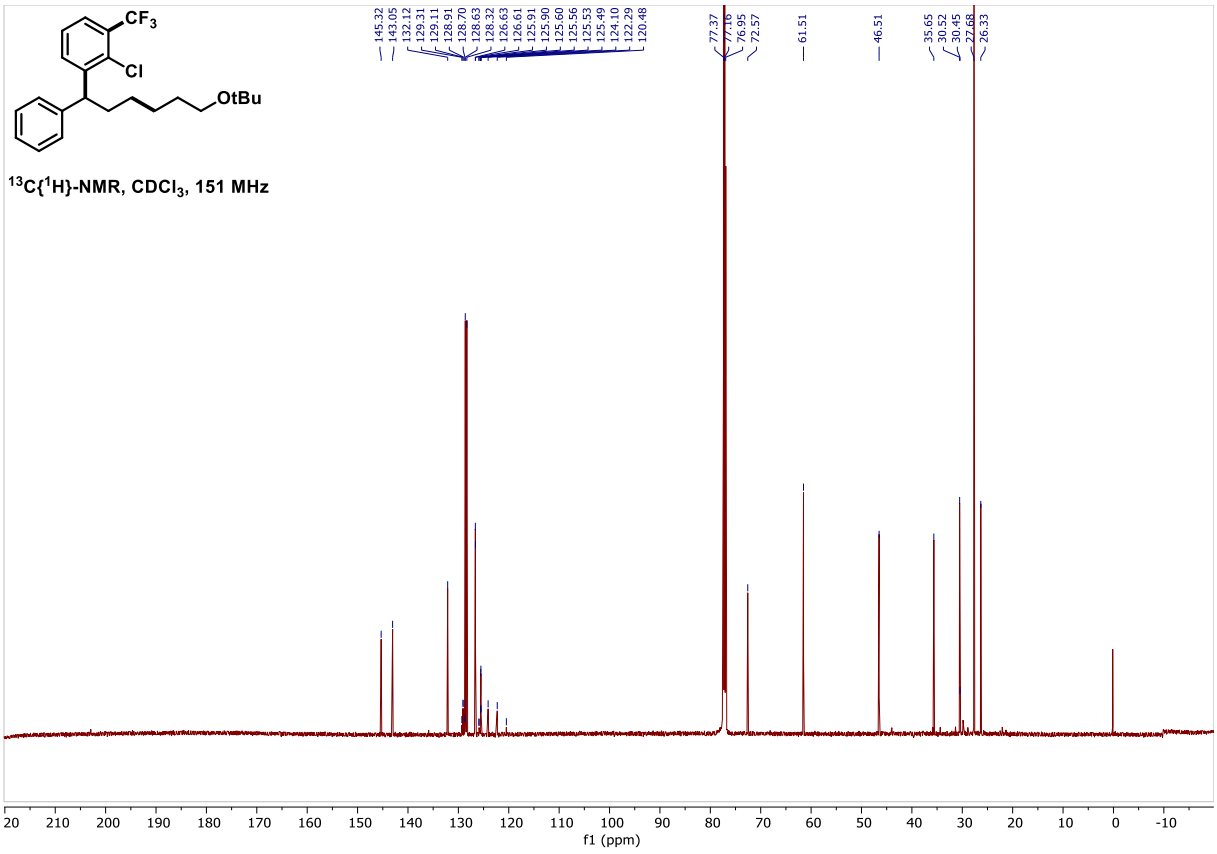




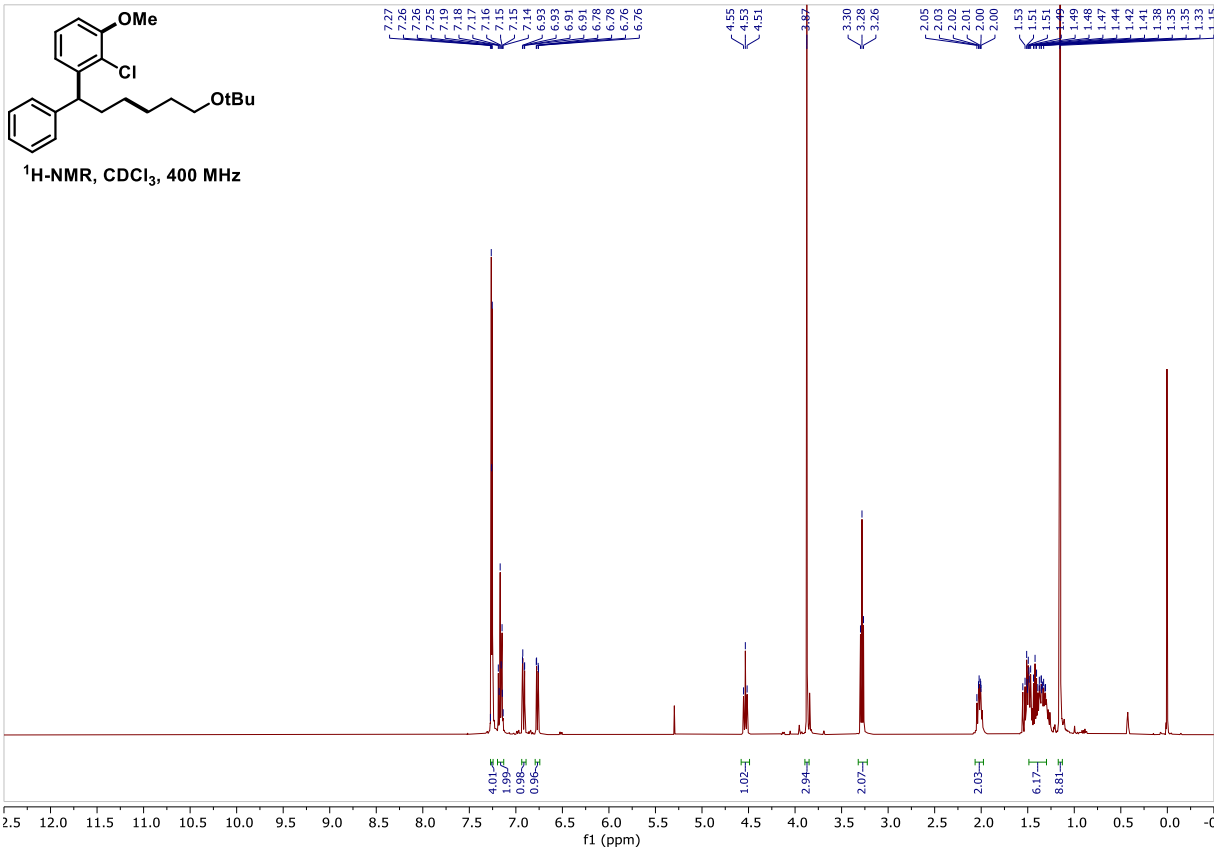
1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-3-(trifluoromethyl)benzene (**3.3s**)

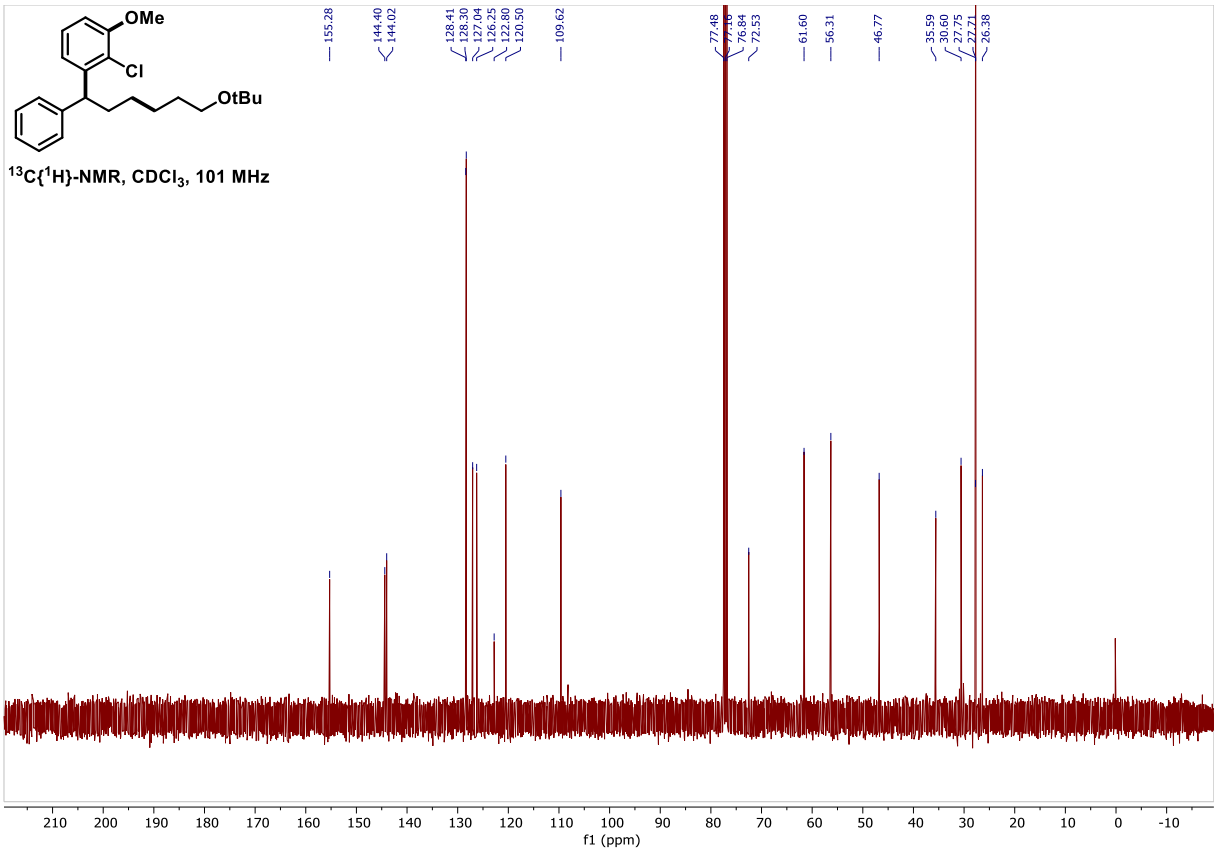




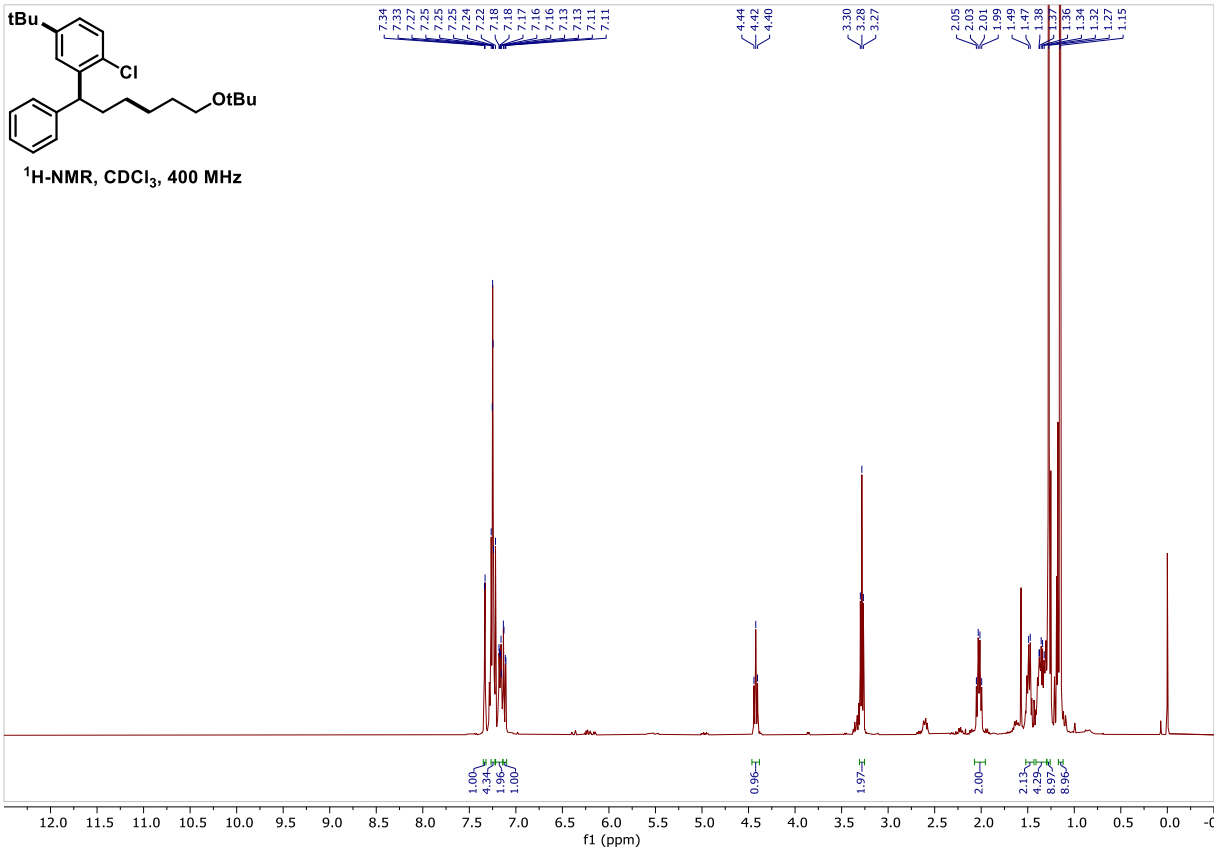


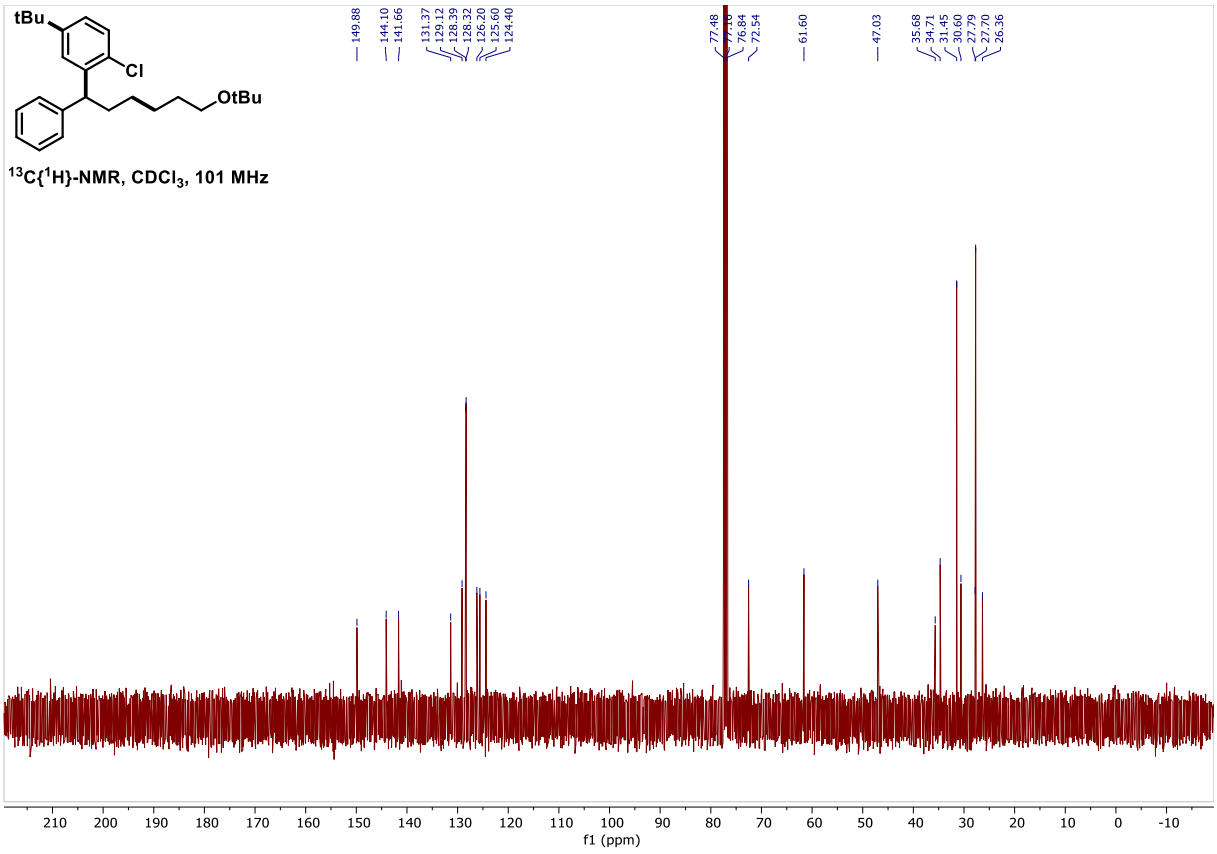
1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-chloro-3-methoxybenzene (**3.3t**)



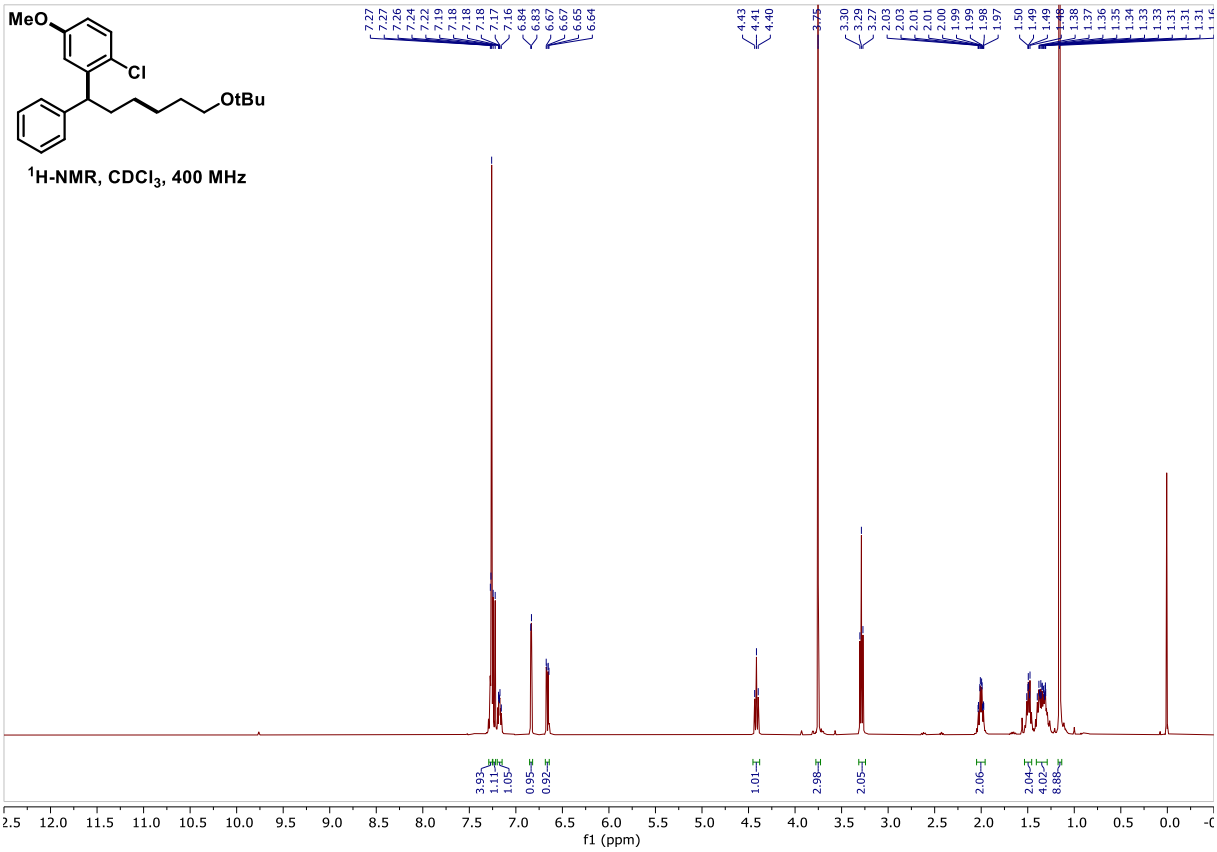


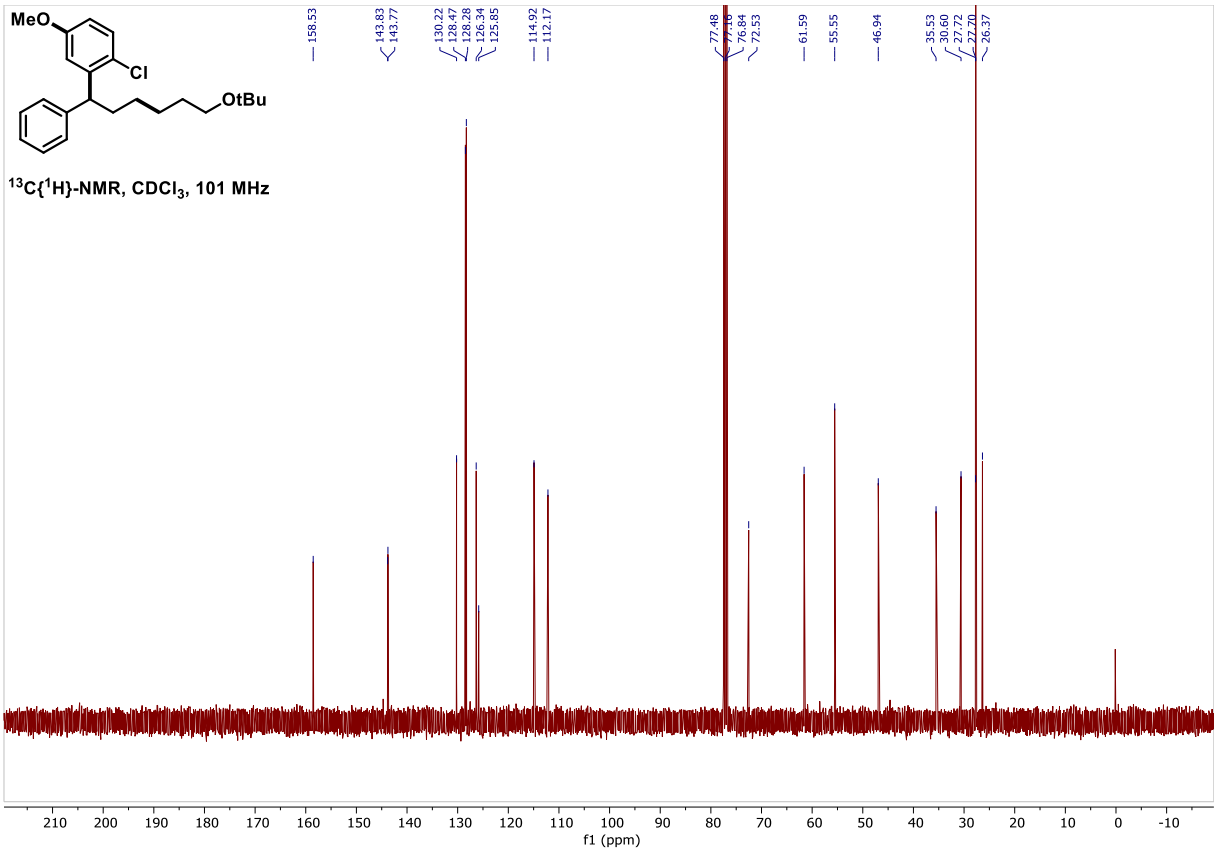
2-(6-(*tert*-Butoxy)-1-phenylhexyl)-4-(*tert*-butyl)-1-chlorobenzene (**3.3u**)



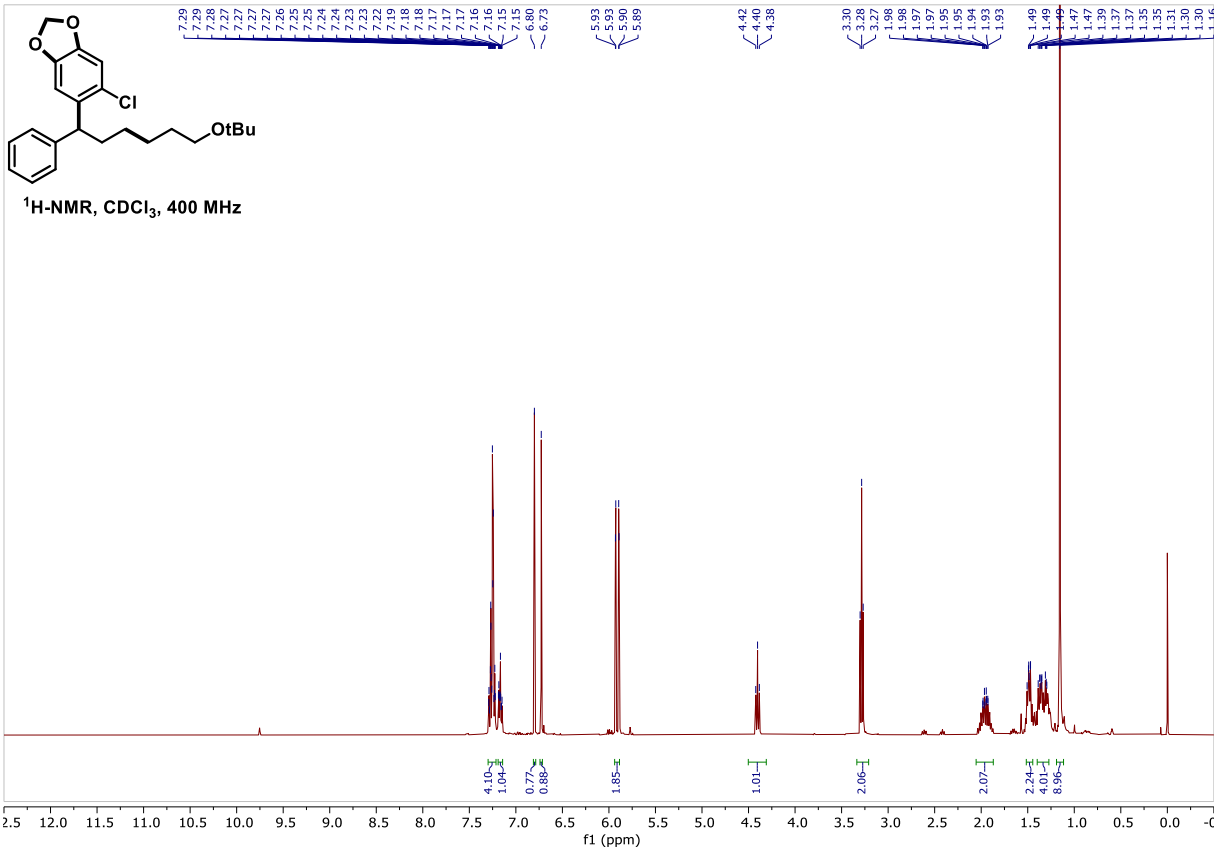


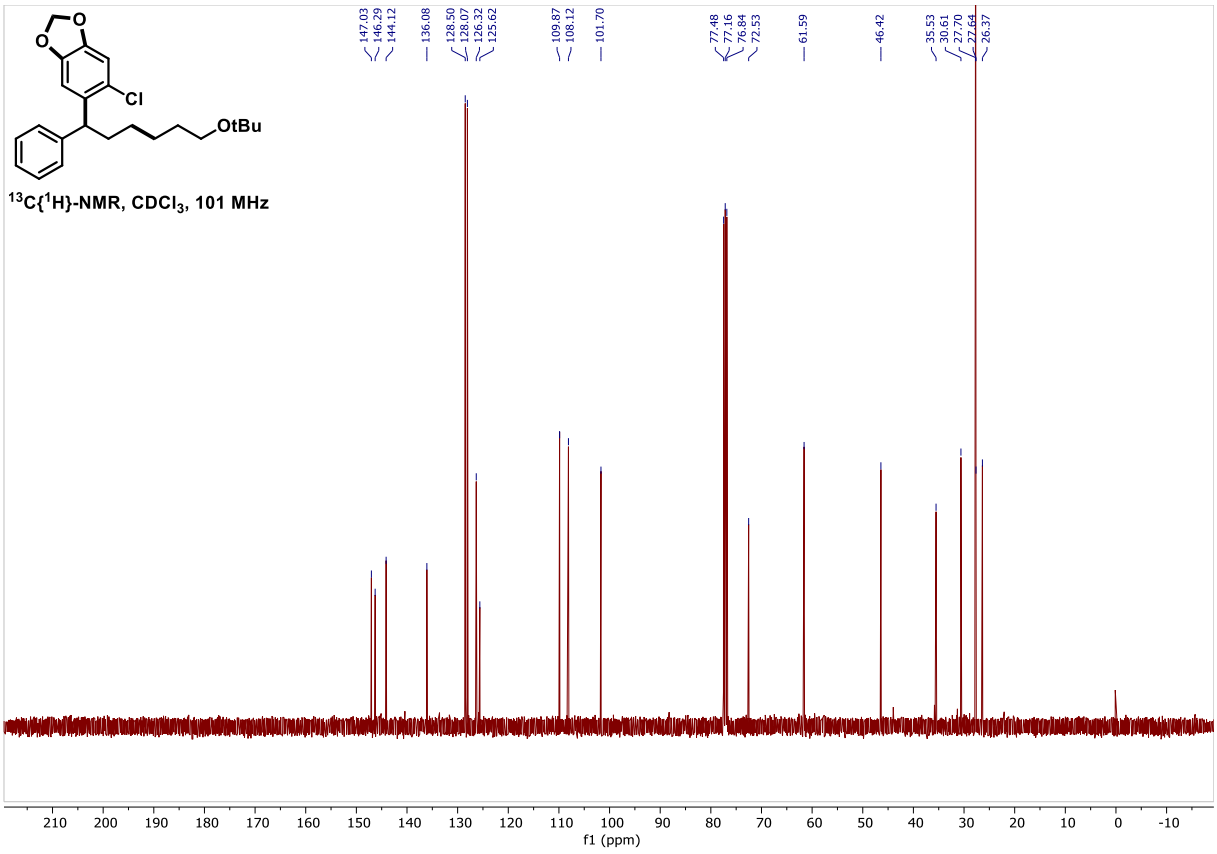
2-(6-(*tert*-Butoxy)-1-phenylhexyl)-1-chloro-4-methoxybenzene (**3.3v**)



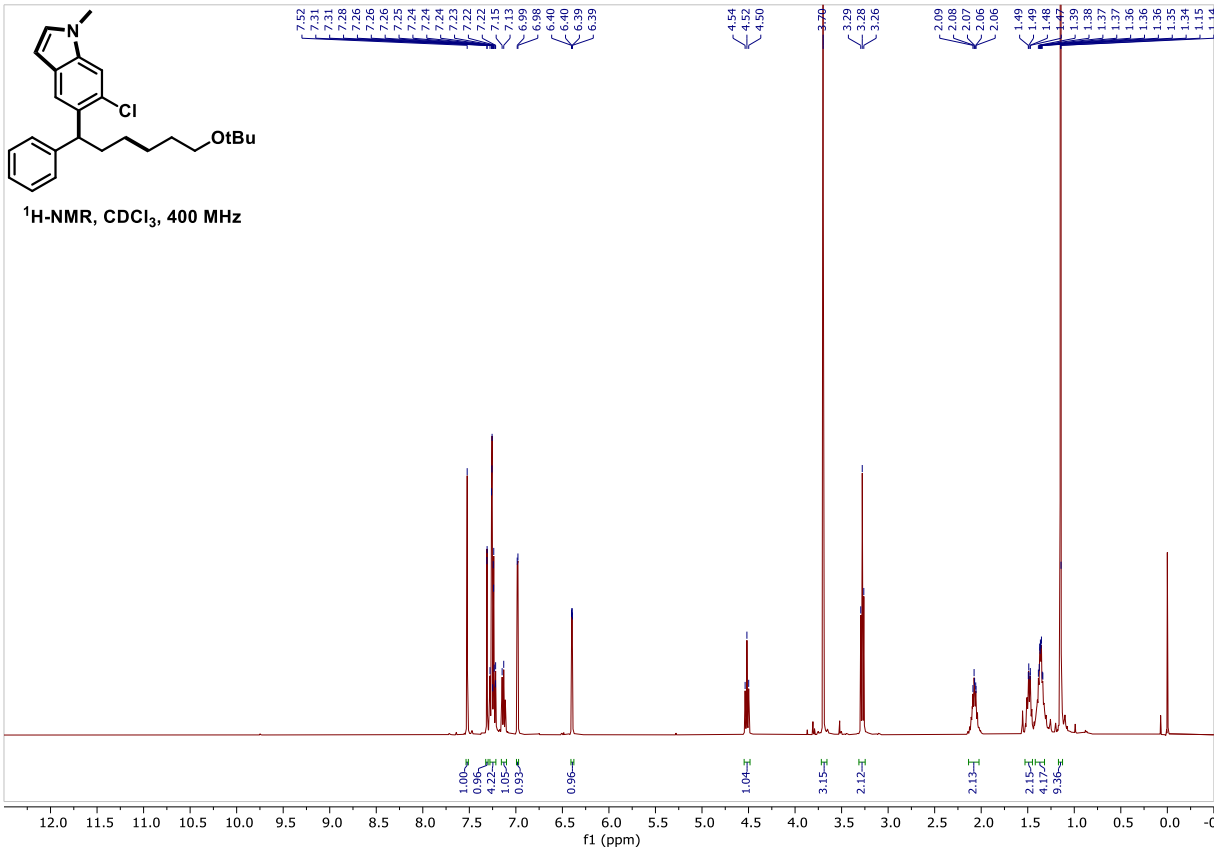


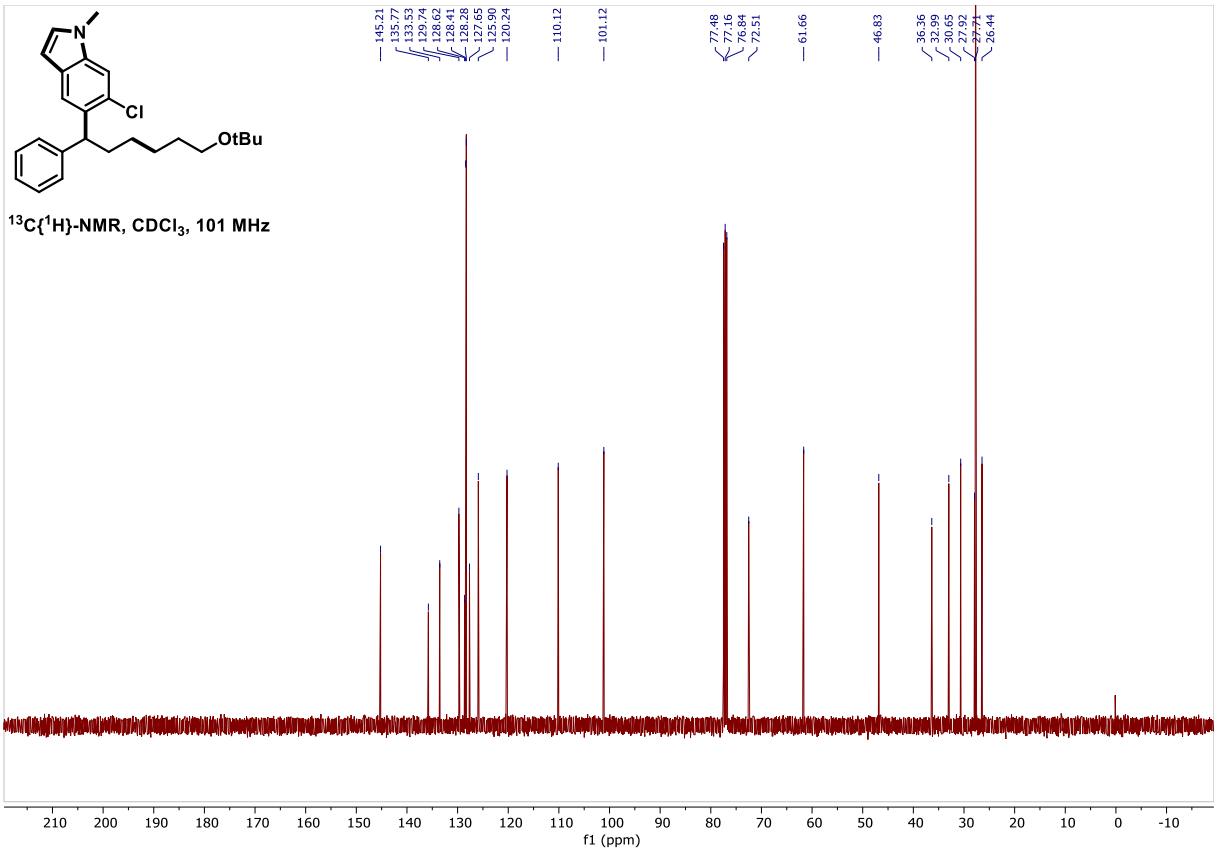
5-(6-(*tert*-Butoxy)-1-phenylhexyl)-6-chlorobenzo-1,3-dioxole (**3.3w**)



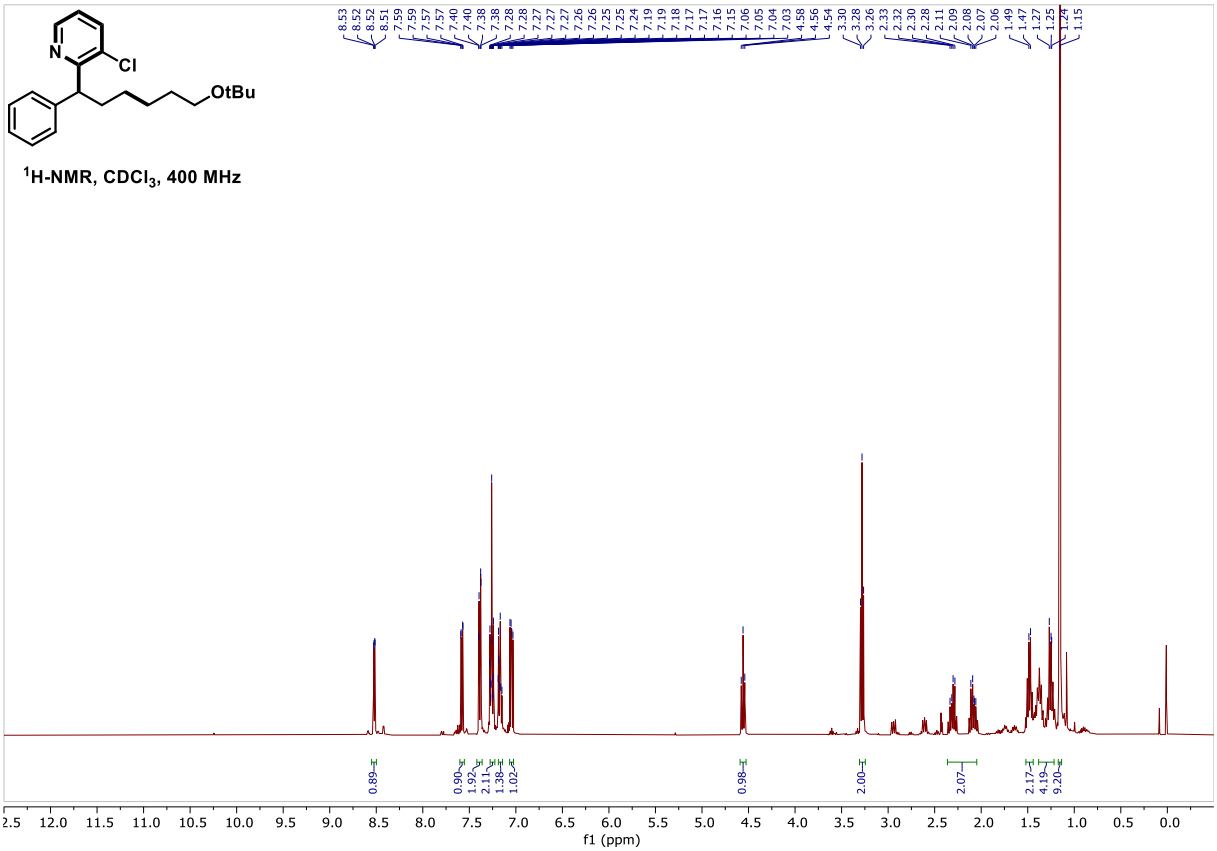


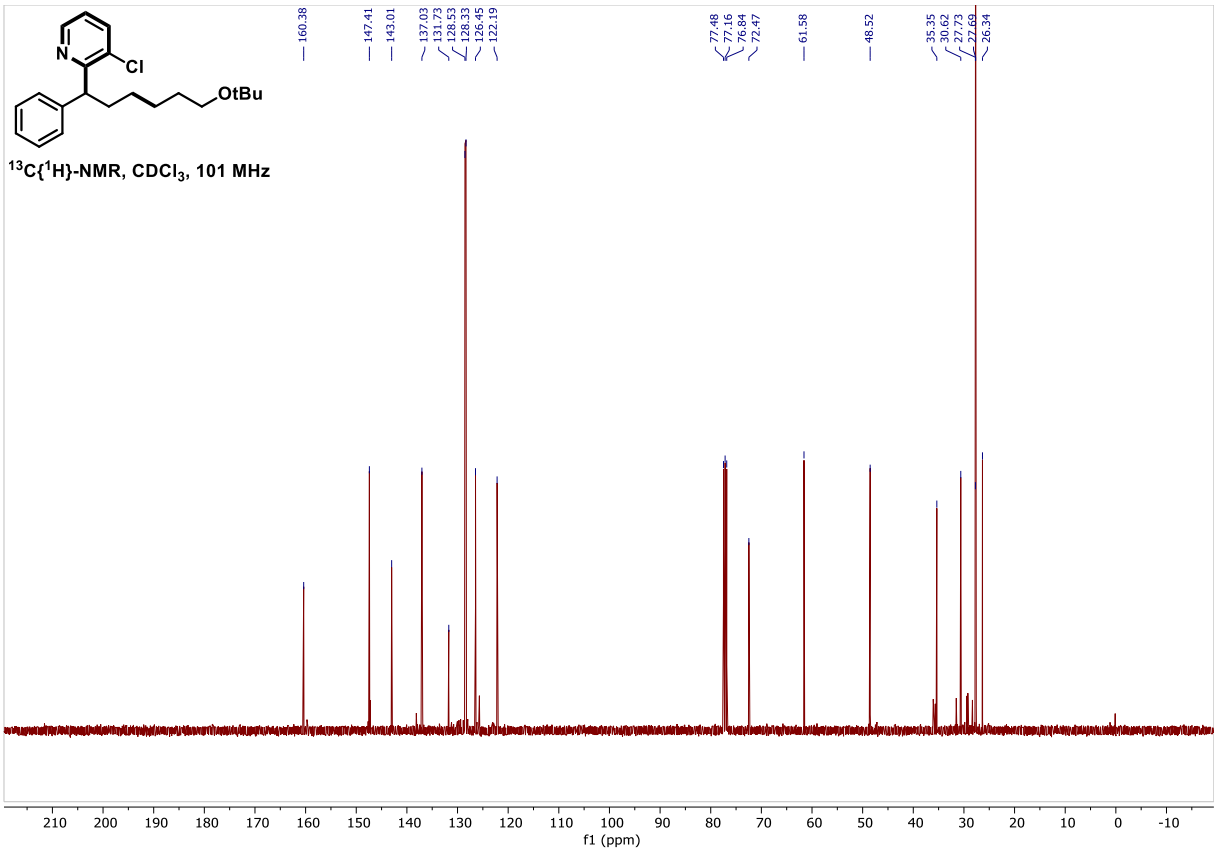
5-(6-(*tert*-Butoxy)-1-phenylhexyl)-6-chloro-1-methyl-1H-indole (**3.3x**)



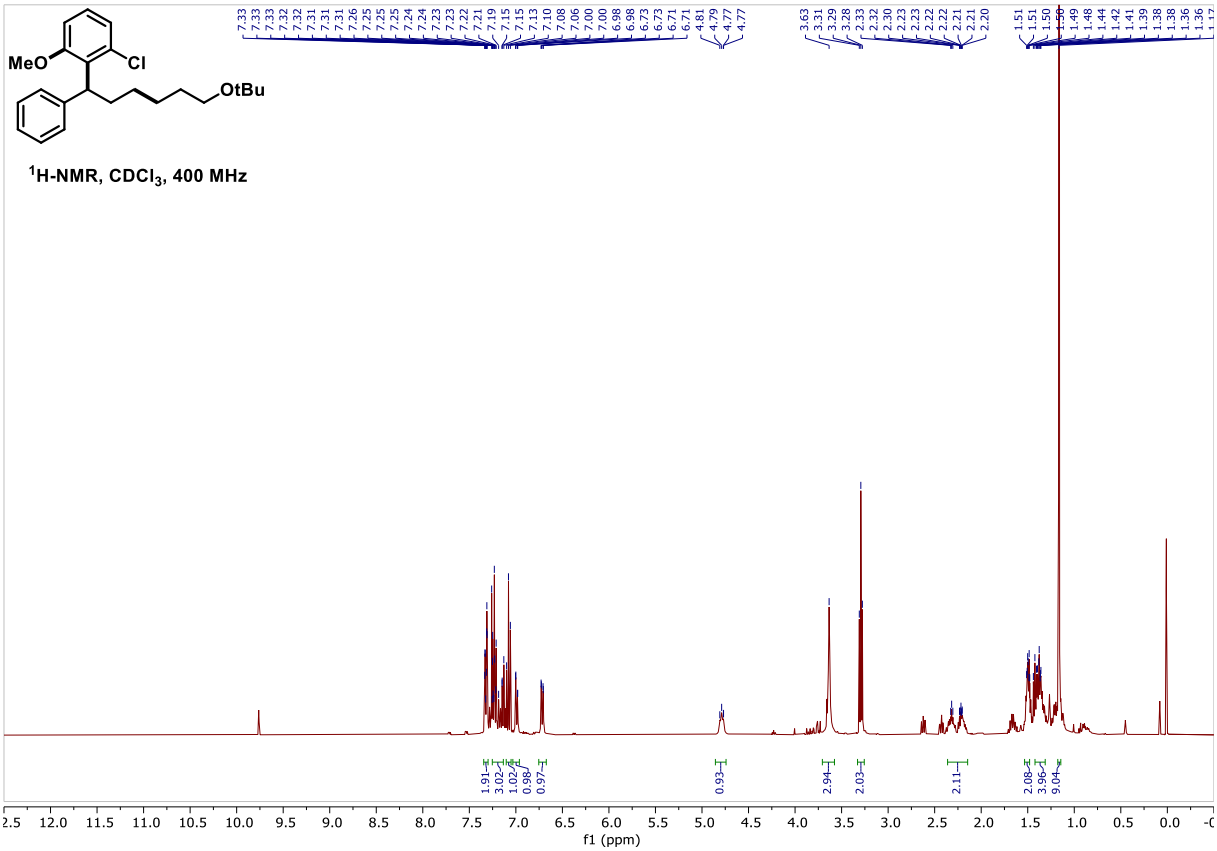


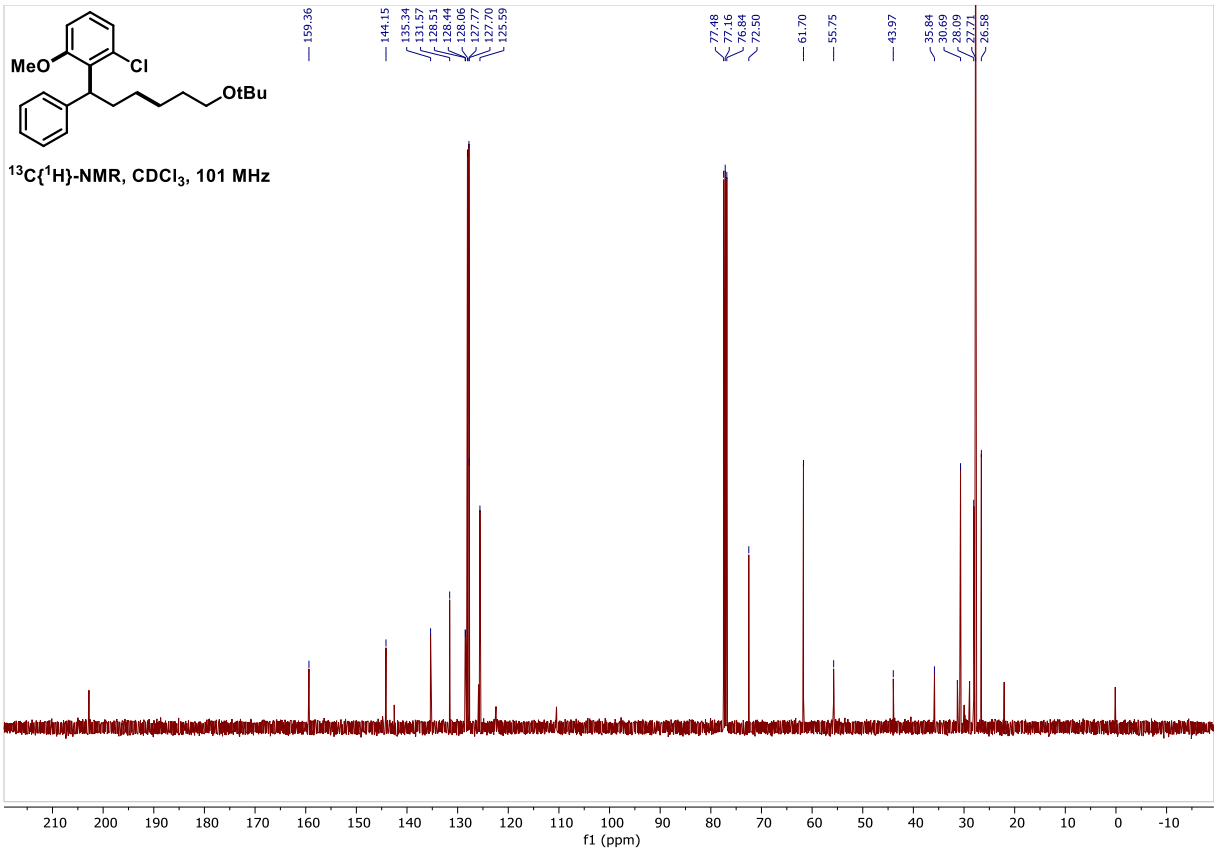
2-(6-(*tert*-Butoxy)-1-phenylhexyl)-3-chloropyridine (**3.3y**)



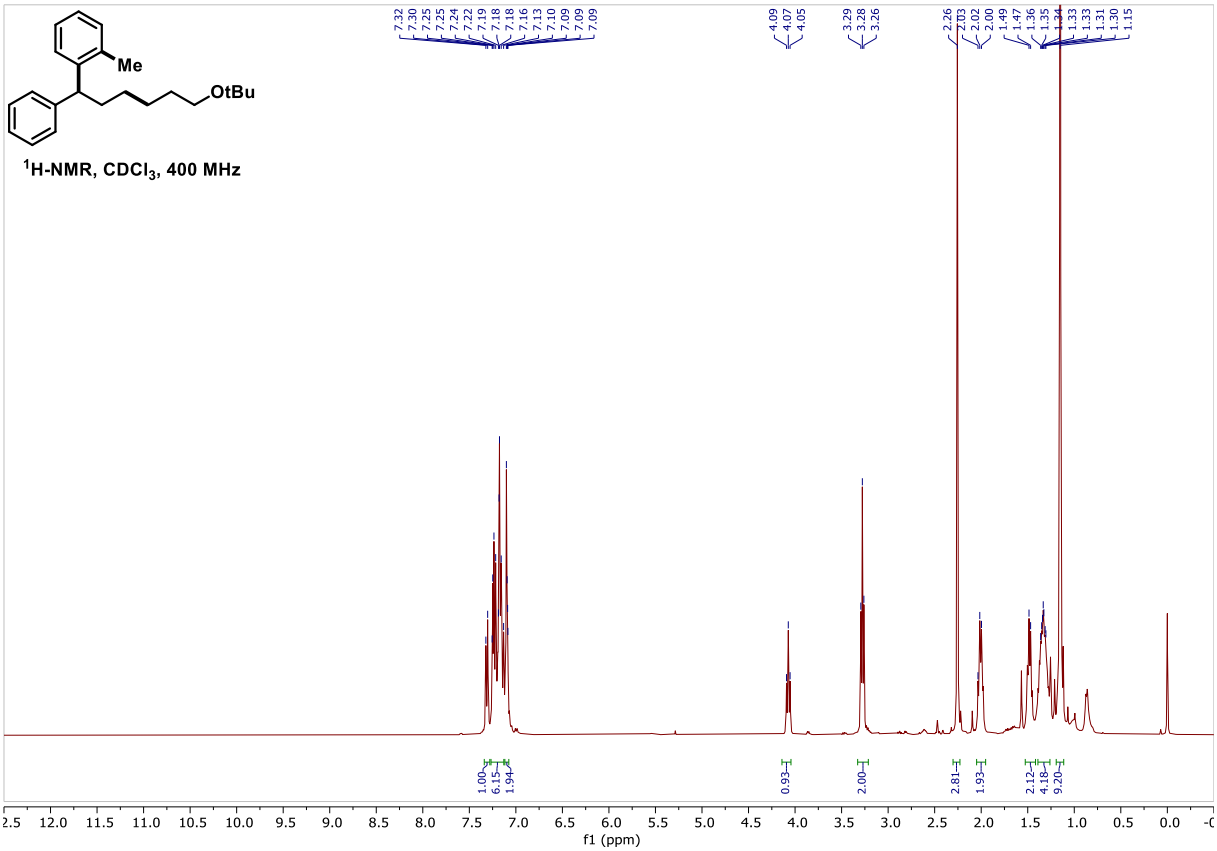


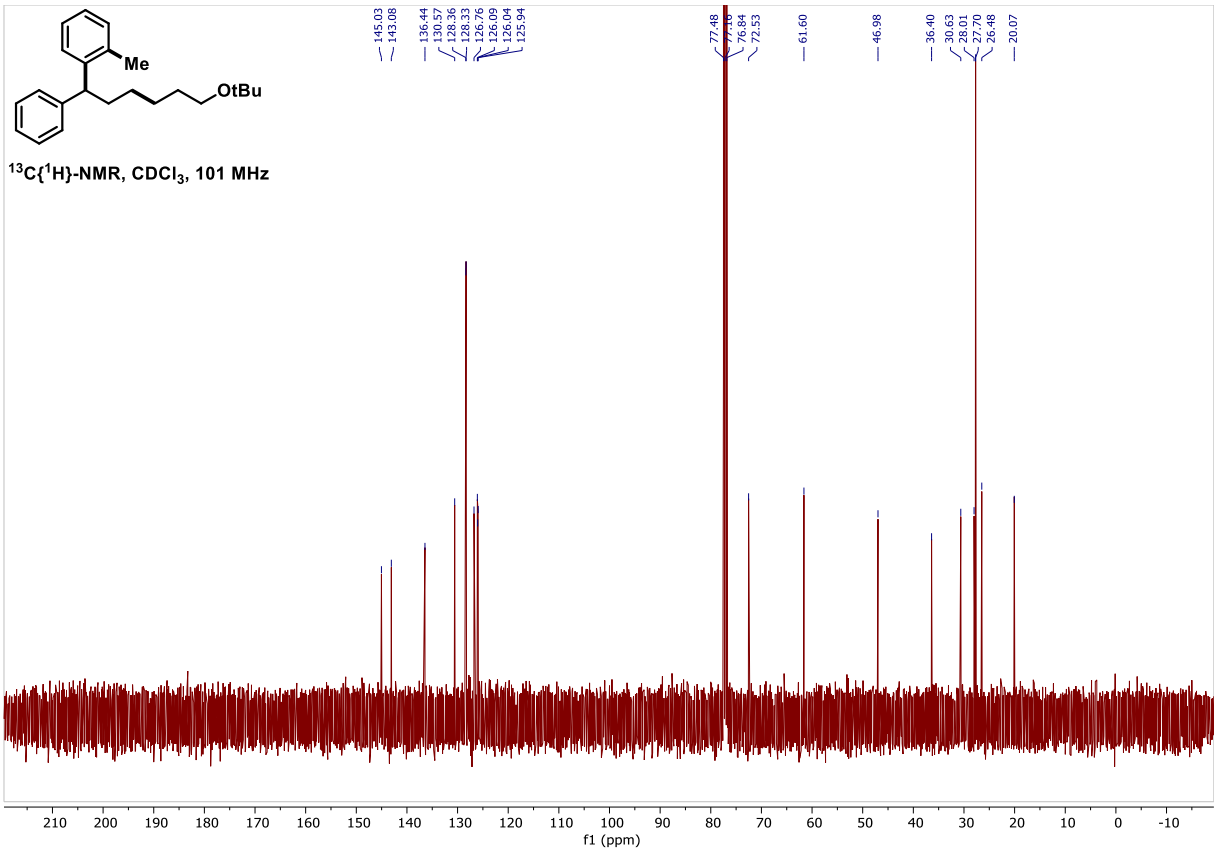
2-(6-(*tert*-Butoxy)-1-phenylhexyl)-1-chloro-3-methoxybenzene (**3.3z**)



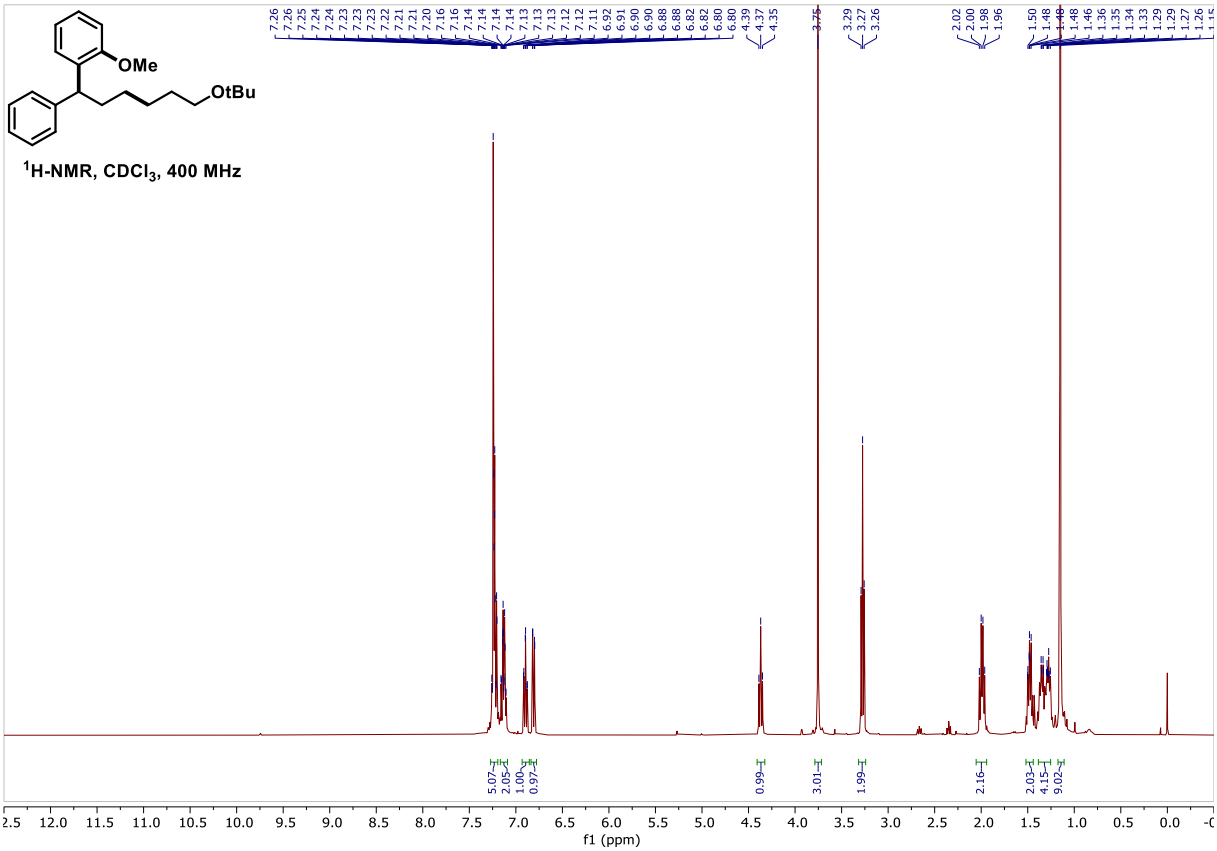


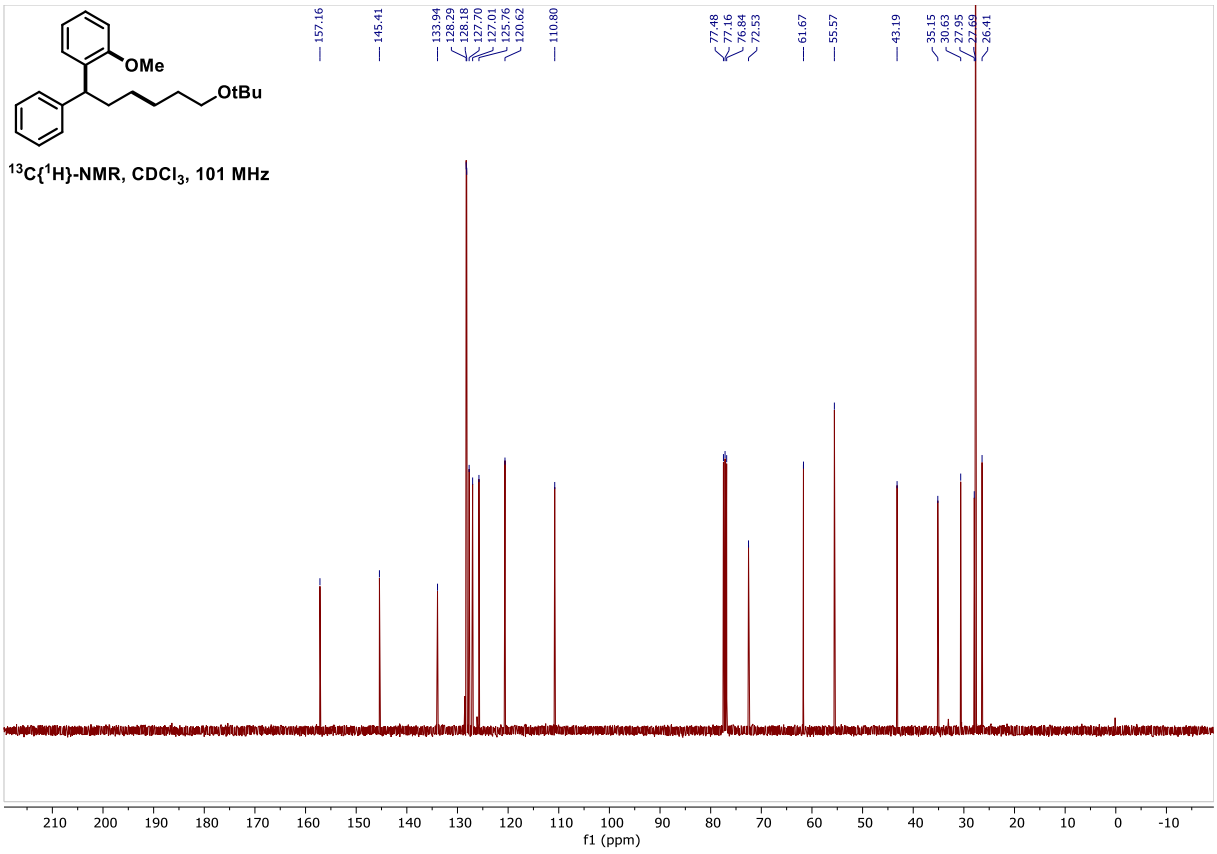
1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-methylbenzene (**3.3aa**)



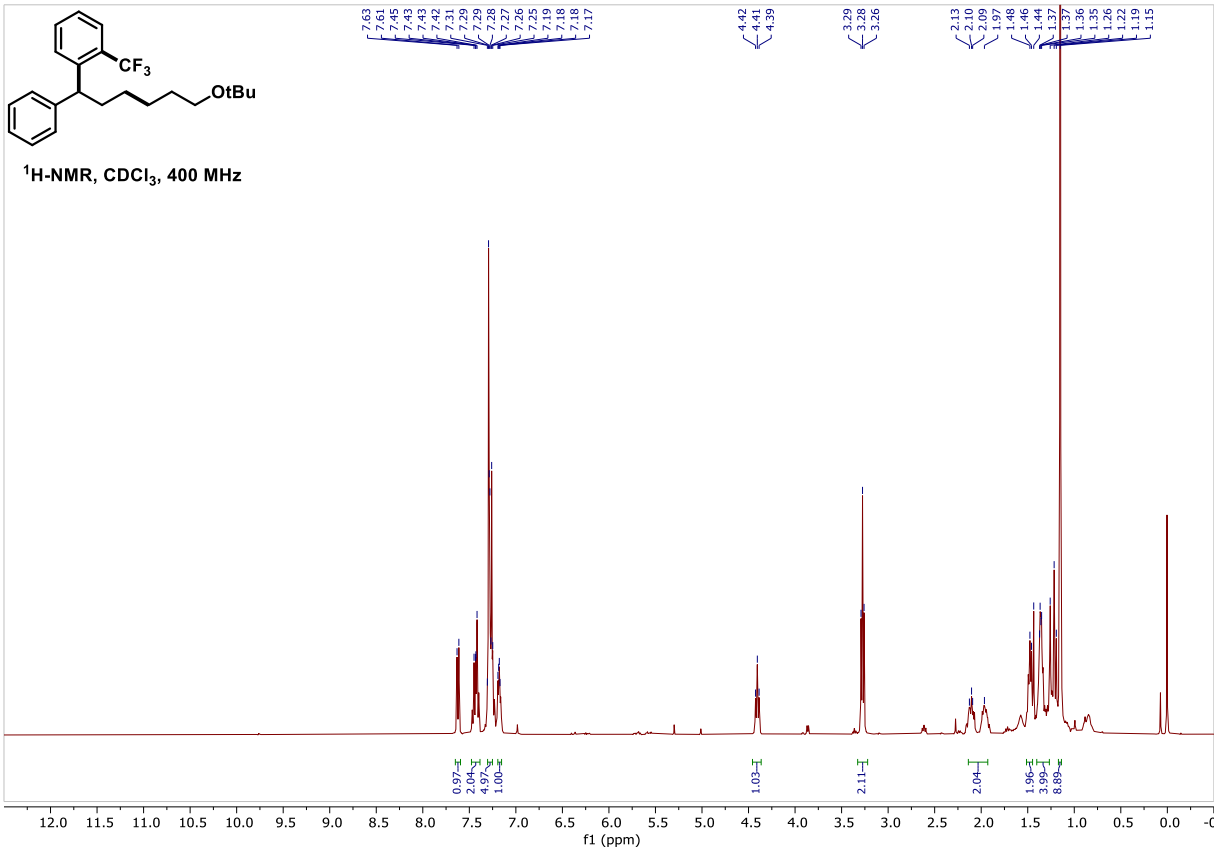


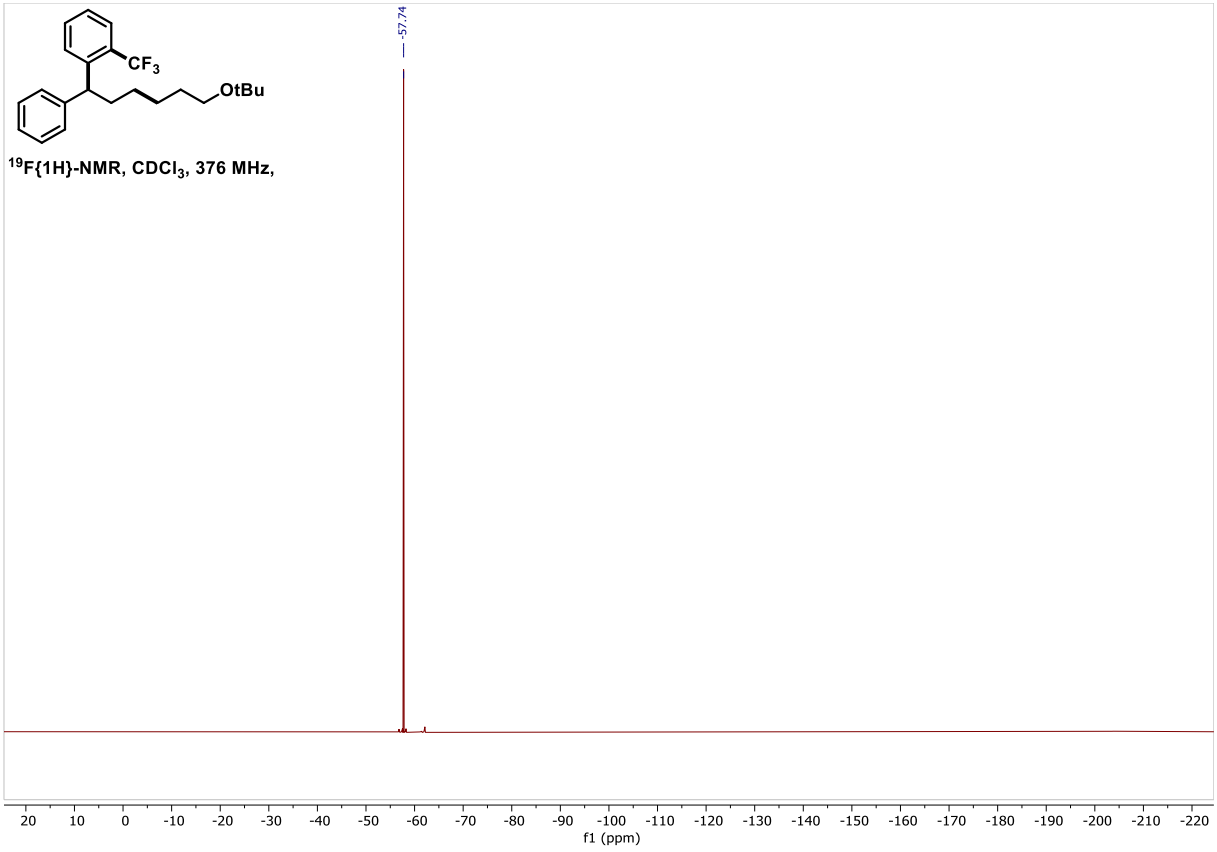
1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-methoxybenzene (**3.3ab**)



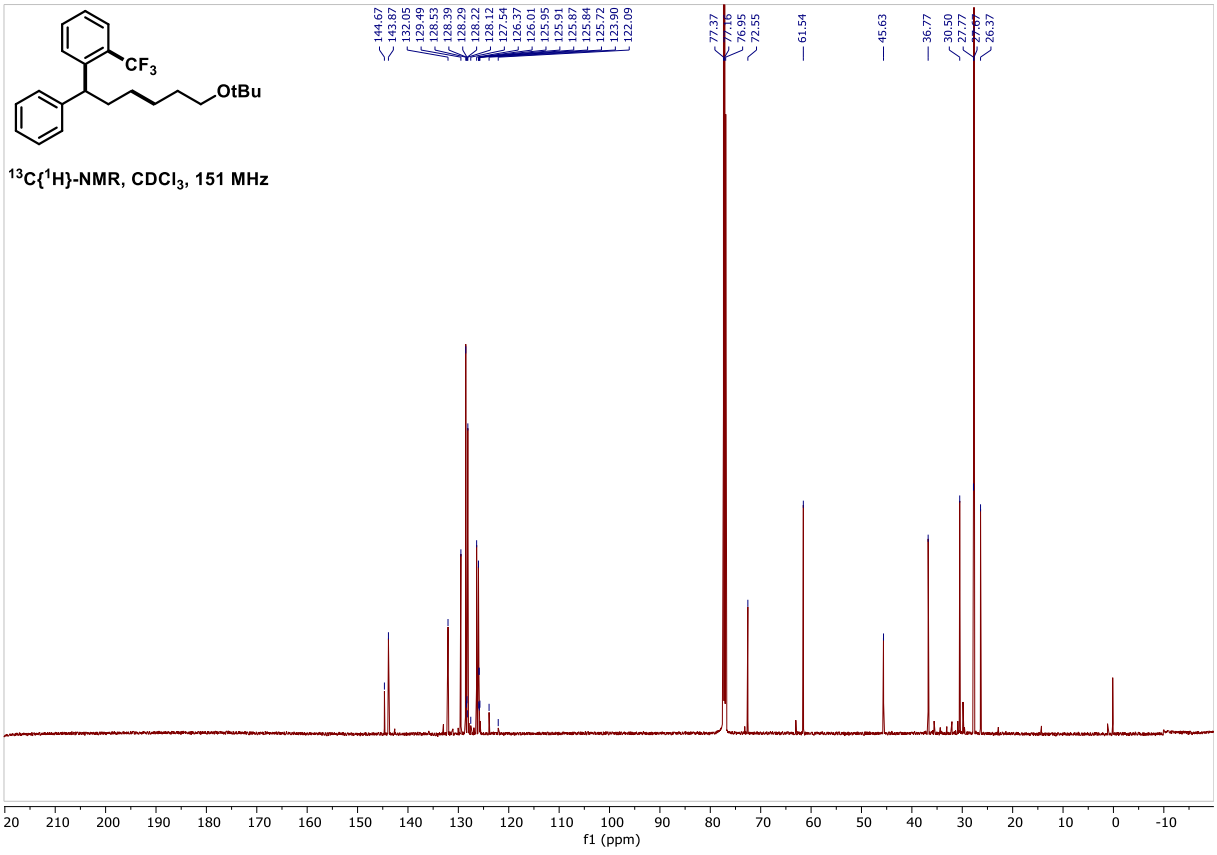


1-(6-(*tert*-Butoxy)-1-phenylhexyl)-2-(trifluoromethyl)benzene (**3.3ac**)



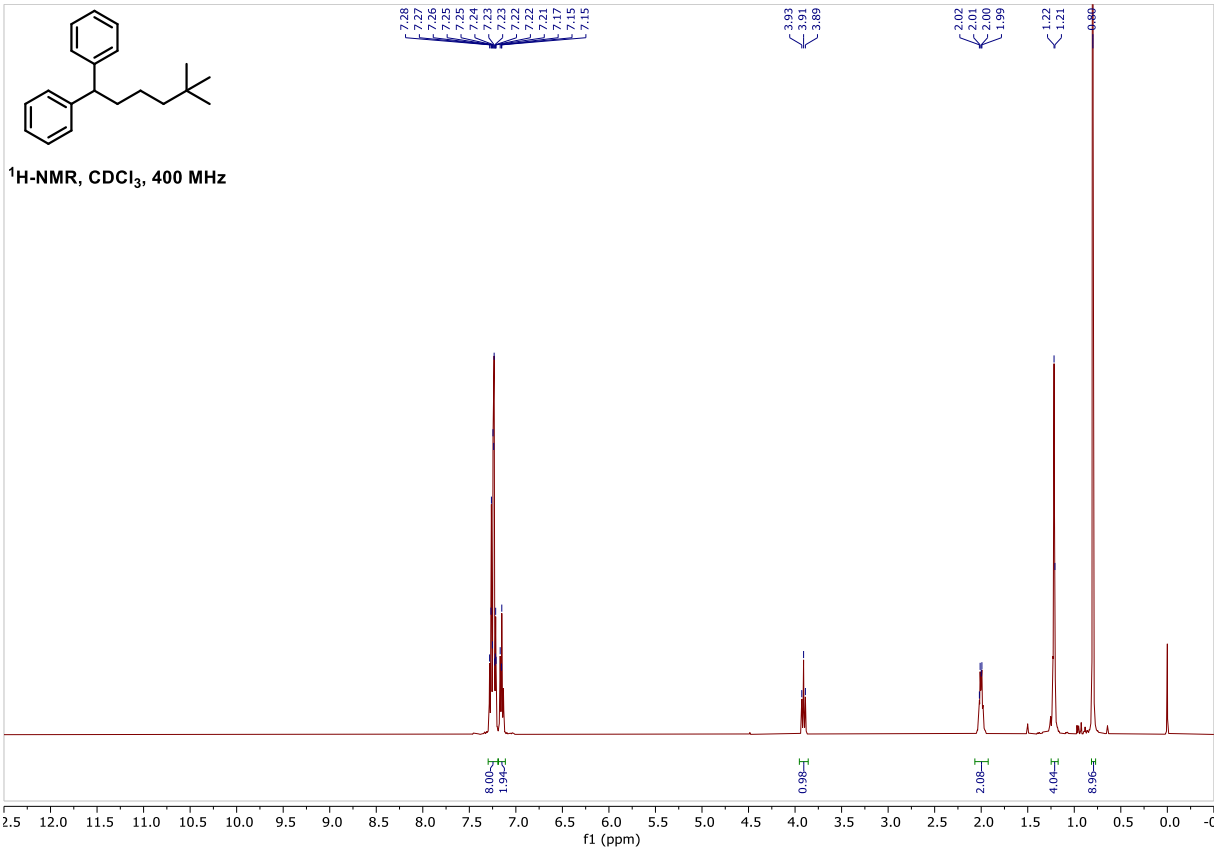


$^{19}F\{^{1}H\}$-NMR, $CDCl_3$, 376 MHz,

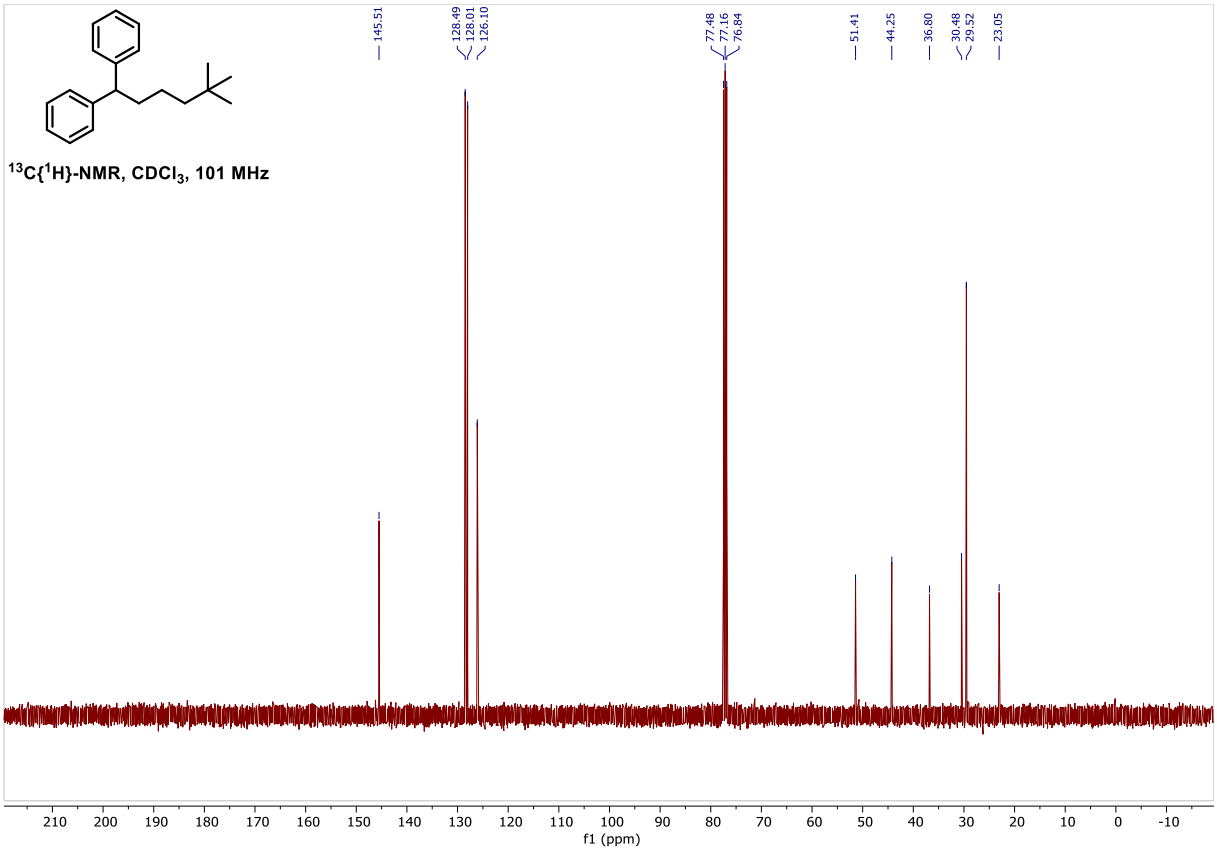


$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 151 MHz

(5,5-Dimethylhexane-1,1-diyl)dibenzene (**3.22**)

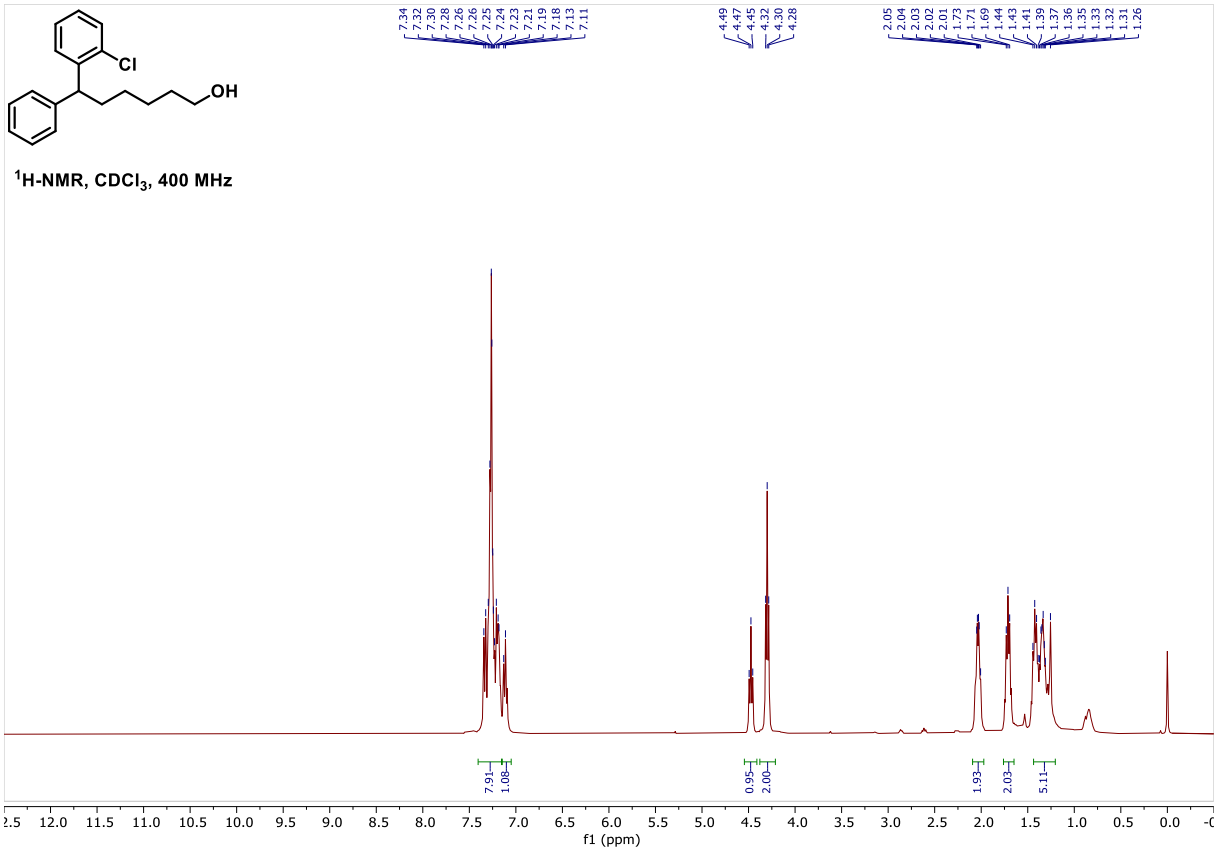


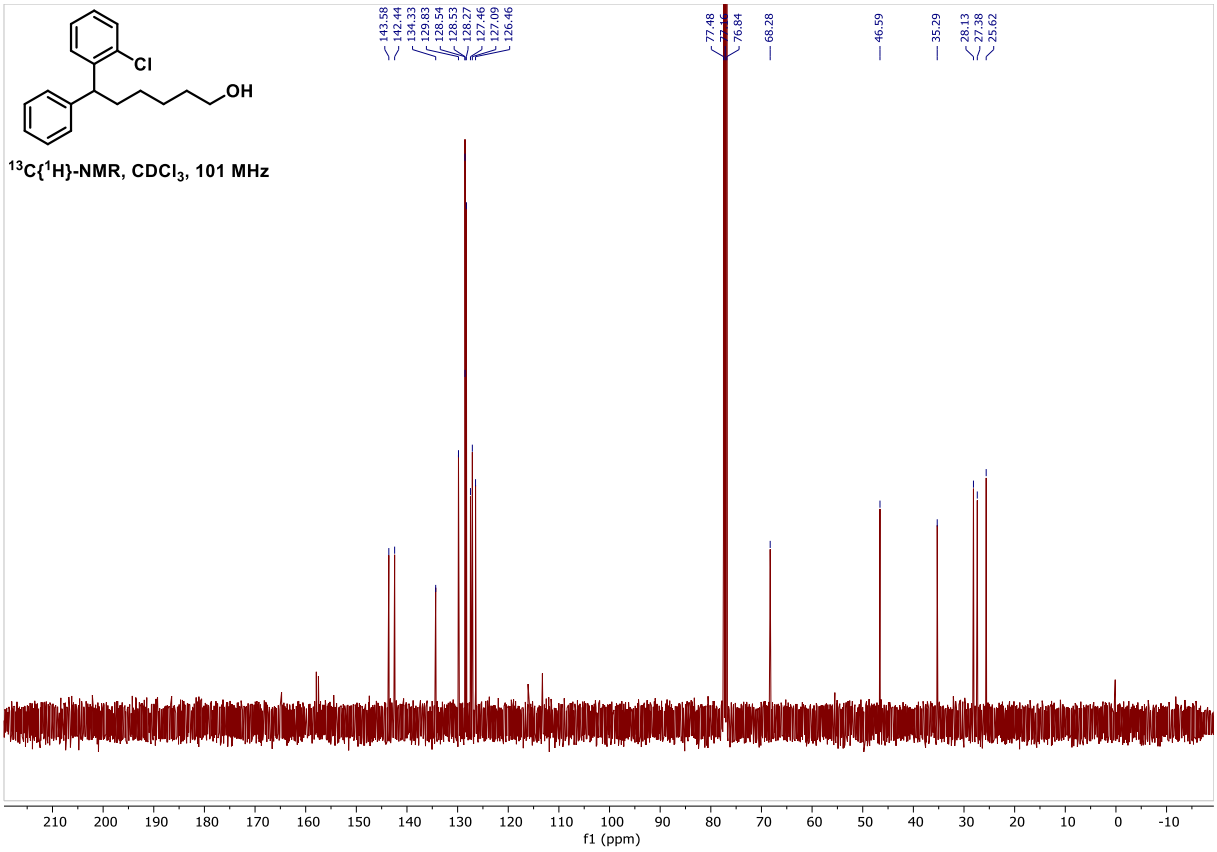
^{1}H-NMR, $CDCl_3$, 400 MHz



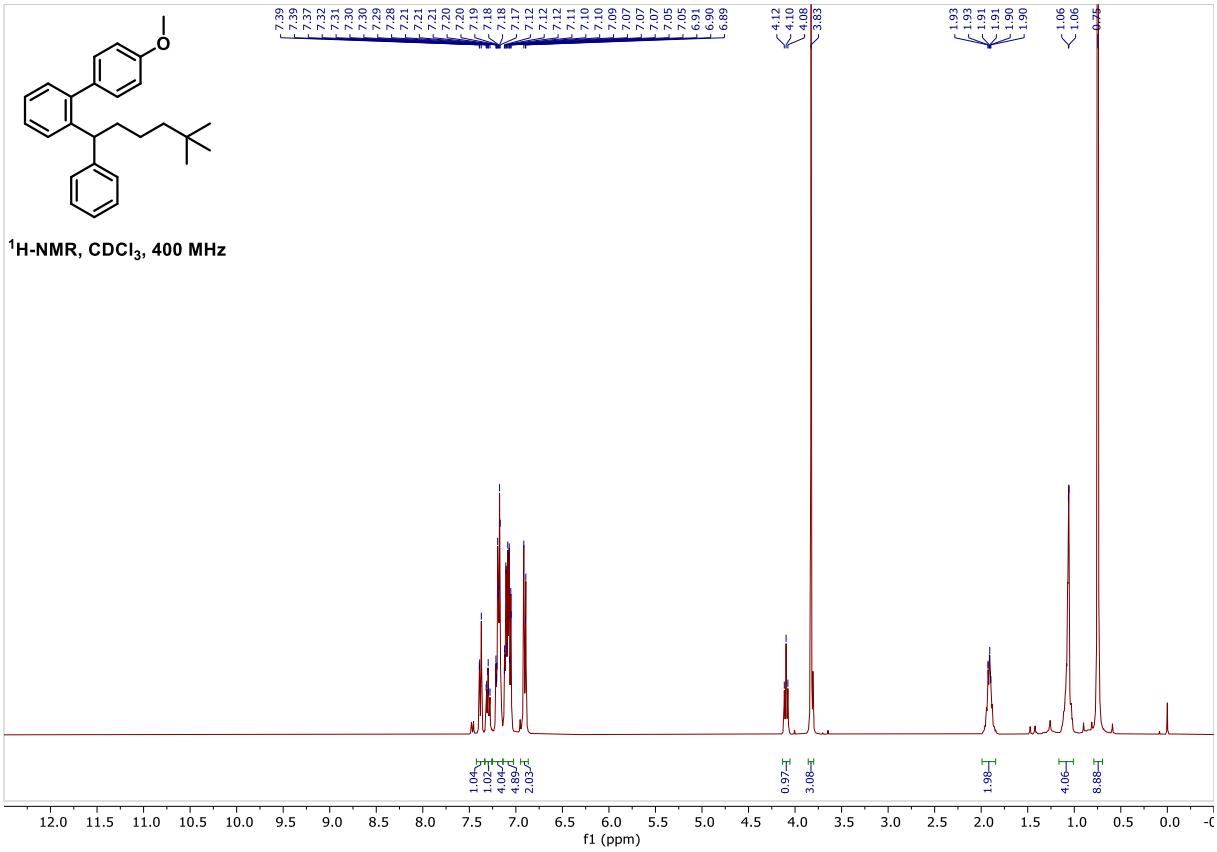
$^{13}C\{^{1}H\}$-NMR, $CDCl_3$, 101 MHz

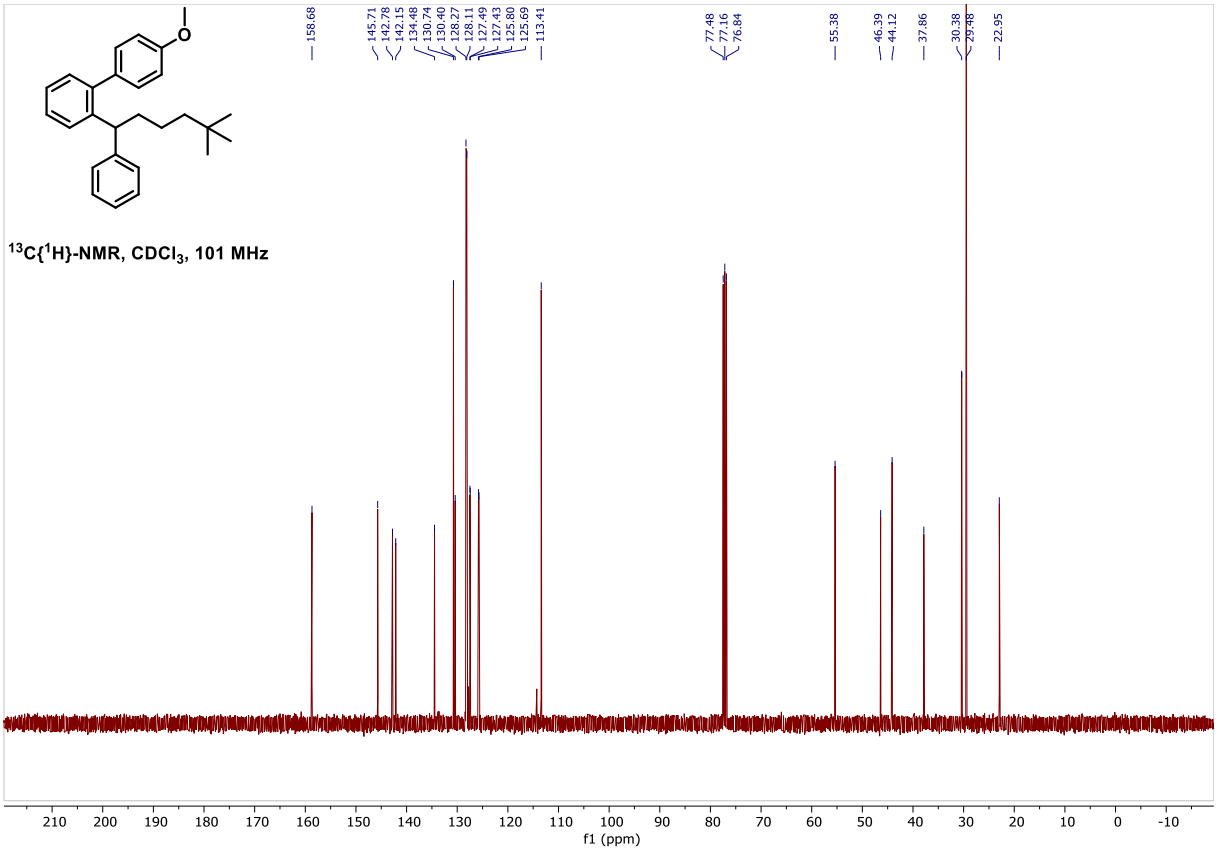
6-(2-Chlorophenyl)-6-phenylhexan-1-ol (**3.23**)



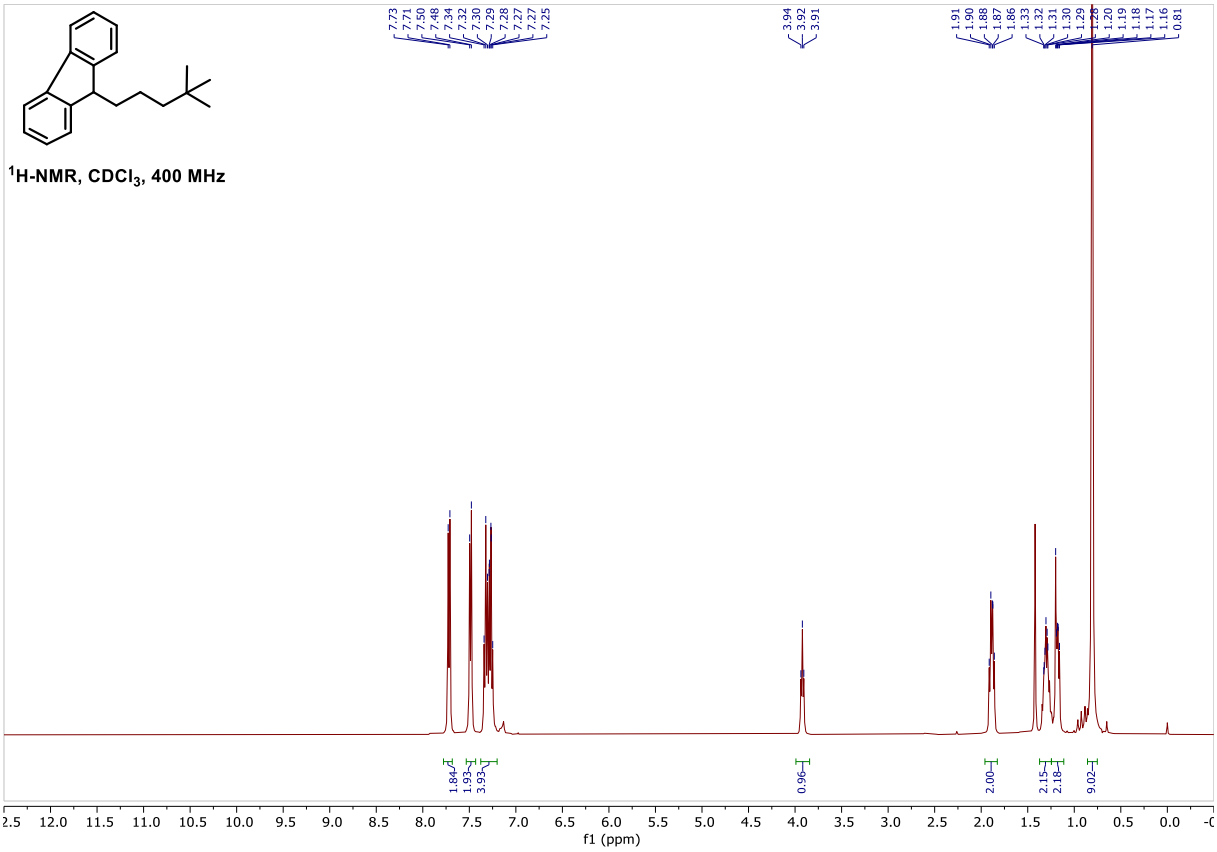


2-(5,5-Dimethyl-1-phenylhexyl)-4'-methoxy-1,1'-biphenyl (**3.24**)

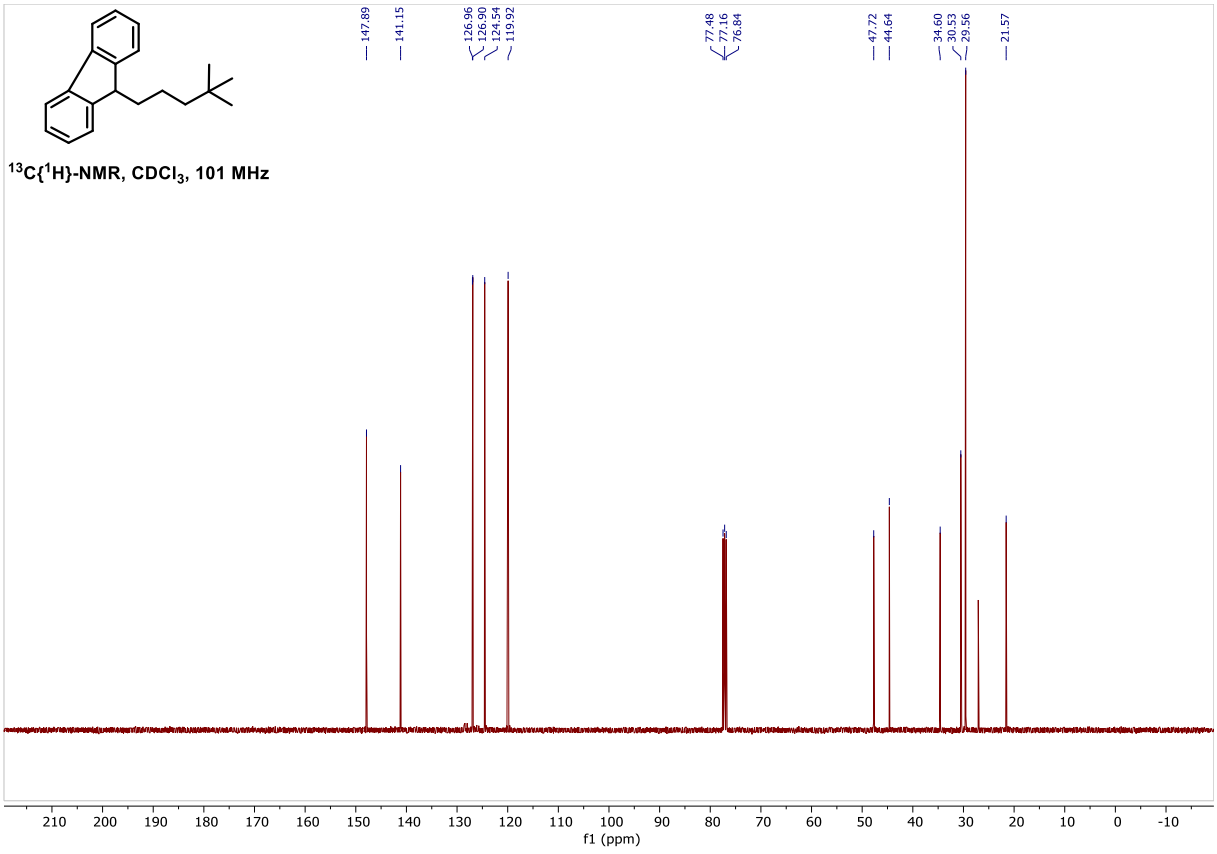




9-(4,4-Dimethylpentyl)-9H-fluorene (**3.25c**)



^{1}H-NMR, $CDCl_3$, 400 MHz



^{13}C{^{1}H}-NMR, $CDCl_3$, 101 MHz